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NUTRITION AND INFECTION

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ON SEVERAL occasions in the Bible, famine and pestilence are mentioned together and the two apocalyptic horsemen still continue to ride in association today. All over the world infectious diseases take their heaviest tolls in the less privileged social classes and in the underdeveloped countries where malnutrition is most prevalent. Likewise, infectious diseases became a large problem in Europe during the last two wars wherever and whenever social disturbances resulted in severe food shortages. These epidemiologic findings are in accord with clinical experience. As is well known, infection is often a serious problem in malnourished individuals, whether malnutrition is the result of lack of certain foodstuffs as in kwashiorkor or of metabolic disorders as in diabetes or in cystic fibrosis of the pancreas.

Suggestive as it is, the evidence provided by epidemiologic and clinical data is not sufficient to prove that nutrition plays an important part in resistance to infection. In social groups as well as in individual patients malnutrition usually occurs in association with other disturbances which may on their own account increase the frequency and severity of infection. Where food is lacking, the social conditions usually lead to crowding and unsanitary practices and thereby facilitate the spread of infectious agents. Metabolic defects which interfere with the utilization of food may decrease resistance to infection through mechanisms which do not have a nutritional basis. In other words, inadequacies in the supply or in the utilization of food are always the secondary consequence of other inadequacies which may be the primary causes of susceptibility to infection, either in the social body or in the individual patient. Because of the difficulties of interpretation inherent in all epidemiologic and clinical correlations, it has not been possible to define clearly the extent to which the nutritional state affects resistance to infection in man. Even in experimental animals the relation between nutrition and infection is not readily established and not well understood. Indeed, as remarked by

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Dr. H. Schneider a few years ago in a critical review of the subject, the belief that the nutritional state affects susceptibility is based more on reiteration than on demonstration. Everyone concerned with this problem is indebted to Dr. Schneider for his searching theoretical analysis of the factors, genetic and environmental, which play a part in the host-nutrition-parasite inter-relationships.[38-40]

Before considering the experimental models which have been devised to study the effect of nutrition on infection, it is important to acknowledge that the experiments have often given conflicting results in the hands of different investigators: witness the divergencies in the conclusions reached concerning the influence of protein intake on susceptibility to various pathogenic agents.[7, 16, 18-20, 22, 25, 26, 32, 39, 47, 49, 52] The very existence of these controversies points to the fact that the relation between nutritional state and infectious process is conditioned by unrecognized or ill-defined factors. Furthermore, dietary constituents can modify resistance and susceptibility in many different ways. We have selected a few experimental situations to illustrate some of the varied mechanisms through which nutrition can affect the manifestations of infectious agents in vivo.

SPECIFIC NUTRITIONAL FACTORS OF RESISTANCE

As is well known, certain dietary factors and in particular vitamins have long been claimed to protect the body against infection. The "anti-infectious" virtues of vitamins A and C still have many advocates among commercial advertisers. While there is no scientific evidence that resistance can be increased by intake of any one of the known vitamins above the level required for a normal state of good nutrition, it has been shown, in contrast, that certain dietary constituents can exert a protective effect against a few pathogens under conditions in which these constituents do not promote growth. A curious illustration of this fact is the increase in resistance to pneumococci and staphylococci exerted by cobalt in mice receiving excessive amounts of manganese in their diet.[17] Recently, suggestive evidence has been adduced in Denmark that greenstuffs which are available in the springtime increase the resistance of guinea pigs to tuberculosis through the agency of substances other than vitamin C and other known nutrients.[4]

The most sophisticated analysis of this aspect of the problem has come from Dr. H. Schneider who has shown that the resistance of mice to salmonellosis can be increased by adding to semisynthetic diets a methanol-soluble material (as yet unidentified) which is present in certain natural foodstuffs. This finding acquires particular significance from the fact that the protective effect can best be detected when the experimental animals and the bacterial pathogens used in the infection tests are genetically heterogeneous, as occurs under natural conditions. It is also worthy of notice that the active substance does not appear to promote growth and that its existence so far has been recognized only through infection tests.[37, 39, 40]

ACTIVATION OF DORMANT INFECTIONS BY NUTRITIONAL DEFICIENCIES

Years ago it was reported that rats fed a diet deficient in some unidentified water-soluble vitamin (then designated H and probably corresponding to biotin) commonly died with pathological changes (pseudotuberculosis) referable to the presence of *Corynebacterium muris*.[12] More recently, it has been found that pseudotuberculosis, often with a fatal outcome, also appeared spontaneously in animals maintained on pantothenate-deficient diets.[43, 56] On the other hand, it is now known that rodents commonly harbor *Corynebacterium muris* in a latent form which rarely, if ever, gives rise to overt disease in normal animals. It is therefore likely that several types of nutritional deficiencies can activate latent infections and in this manner cause microbial disease. Thus, famine can indirectly pave the way for pestilence.

THE INFLUENCE OF INTAKE OF PROTEIN AND AMINO ACIDS ON EXPERIMENTAL INFECTIONS

Like human beings, animals in a state of profound nutritional deficiency are highly susceptible to experimental infections. Protein deficiency seems to be of particular importance in this regard, as observed in kwashiorkor and in the exudative type of tuberculosis so frequently observed in populations deprived of "animal" protein. While these facts are generally accepted, little knowledge is available concerning the effects to be expected when the protein intake, while being lower than that required for maximum growth, is sufficient to be compatible with the maintenance of an acceptable physiological state. Experiments designed to deal with this problem have been carried out during recent years in our laboratory.[7, 36]

Young mice were fed ad lib. for 1 to 2 weeks semisynthetic diets which differed in the concentration and the composition of their protein and amino acid constituents but otherwise contained optimum amounts of all other known growth factors. The animals were then infected with adequate doses of various types of bacteria (tubercle bacilli, staphylococci, Friedländer bacilli, etc.). The intravenous route was used for most of the infection tests, but more recently administration of tubercle bacilli by aerosol has also been used successfully.[36]

Under all conditions of test it was found that following infection mice fed diets containing 20 per cent casein survived longer than did mice receiving the same diets but with only 8 or 5 per cent casein. It is of great interest that noninfected mice gained weight just as rapidly on 8 per cent as on 20 per cent casein. In other words, the difference in resistance to infection elicited by 8 versus 20 per cent casein could not have been predicted from the respective growth curves on these two diets[7] (for examples, see Tables I and II).

The resistance of mice receiving 8 or 5 per cent casein could be rendered equal or superior to that of mice receiving 20 per cent casein by supplementing the two low protein diets with adequate mixtures of essential amino acids (Table II). This increase in resistance was achieved even though the animals on the amino acid diets

ate less avidly than did those receiving the 20 per cent casein diet and therefore gained weight less rapidly. Here again, resistance to infection could not have been predicted from the diet, qualitative factors also influence the course of the infectious processes. Even with large concentrations of protein, resistance to infection was decreased when one or

TABLE I. EFFECT OF DIETARY PROTEIN ON SUSCEPTIBILITY OF MICE TO TUBERCULOSIS

DIET (14 DAYS BEFORE INFECTION)	WEIGHT PER ANIMAL (GM.)			CUMULATIVE DEATHS AT INDICATED DAYS POSTINFECTION			
	ORIGINAL	AT INFECTION TIME	GAIN	21	28	35	42
				(out of 16 mice)			
20 C*	26.1	32.0	5.9	1	4	7	9
8 C†	26.4	31.1	4.7	5	14	15	16
Pellets‡	26.1	29.8	3.7	4	15	15	16

Male mice; infected in vivo with 0.1 ml. *Myco. tuberculosis* (Vallée).
*A complete diet containing 20 per cent casein.
†A complete diet containing 8 per cent casein.
‡Commercial pellets are claimed to contain 21 per cent "crude protein," but a large part of these pellets consists of unspecified plant material.

the growth curves of uninfected animals.[7] It is of interest to mention here that other investigators working with more complex and less well-defined diets have also recognized that more of the essential amino acids was lacking or when their concentration was critically low. Thus, in diets containing as sole source of protein either gelatin, gluten, gliadin, or soy bean α

TABLE II. EFFECT OF AMINO ACIDS ON SUSCEPTIBILITY TO INFECTION

DIET (8 DAYS BEFORE INFECTION)	WEIGHT PER ANIMAL (GM.)			CUMULATIVE DEATHS AT INDICATED DAYS POSTINFECTION				
	ORIGINAL	AT INFECTION TIME	GAIN	3	5	14	21	28
					(out of 8 mice)			
20 C*	14.3	18.1	3.8	0	3	3	3	4
8 C†	13.5	17.7	4.2	3	4	5	6	8
8C + AA‡	13.7	13.7	0.0	0	0	0	0	0
(16 DAYS BEFORE INFECTION)				4		7		14
						(out of 16 mice)		
20 C*	14.1	?	?	2		4		6
8 C†	14.1	22.2	8.1	3		10		12
8C + AA‡	13.9	17.9	4.0	0		1		2

Female mice; fed 2 days (after weaning) on bread and milk before being placed on experimental diets; infected in vivo with 0.05 ml. *Myco. fortuitum* (Penso).
*A complete diet containing 20 per cent casein.
†A complete diet containing 8 per cent casein.
‡A complete diet containing 8 per cent casein, supplemented with 12 per cent of a balanced mixture of essential amino acids.

the regimens which prove best for growth and reproduction are not necessarily those most favorable for resistance to infection.[4, 19]

Along with the quantitative aspects of the protein concentration in protein caused enhancement of infection (Tables III and IV). In contrast, resistance was high when the animals were fed a mixture of rice and soy bean in a proportion designed to provide an amino acid pattern similar

to that present in casein[36] (Table V). Thus, the information available at present suggests that the proper balance of amino acids is even more important than their total amount in determining resistance to infection. However, much work remains to be done to determine what amino acids are of particular importance in this regard.

TABLE III. EFFECT OF DIETARY PROTEIN ON SUSCEPTIBILITY TO INFECTION

PROTEIN (PER CENT)	TIME ON DIET (DAYS)	AVERAGE WEIGHT CHANGE	NUMBER OF MICE	CUMULATIVE DEATHS AT INDICATED DAYS POSTINFECTION		
				3	5	7
Casein 20*	7	+3.1	7	2	2	7
Casein 5†	7	−2.1	8	6	7	8
Gluten 20‡	7	+1.7	8	3	5	8
Casein 20	15	+6.1	8	1	3	6
Casein 5	15	−3.4	8	6	7	8
Gluten 20	15	+3.4	7	4	5	7
Casein 20	21	+7.5	7	3	3	5
Casein 5	21	−3.2	7	7	7	7
Gluten 20	21	+1.8	8	6	6	8

Mice infected with 0.05 ml. *Staph. aureus* in vivo.
*A complete diet containing 20 per cent casein.
†A complete diet containing 5 per cent casein.
‡A complete diet containing 20 per cent gluten as sole source of protein.

TABLE IV. EFFECT OF DIETARY PROTEIN ON SUSCEPTIBILITY TO INFECTION

PROTEIN (PER CENT)	AVERAGE WEIGHT CHANGE	NUMBER OF MICE	CUMULATIVE DEATHS AT INDICATED DAYS POSTINFECTION		
			17	21	25
Casein 20*	+3.6	15	3	9	15
Casein 5†	−4.6	15	11	15	—
Gluten 20‡	−2.8	14	7	14	—

Animals maintained on diets for 15 days before infection with 0.2 ml. *Myco. tuberculosis* in vivo.
*A complete diet containing 20 per cent casein.
†A complete diet containing 5 per cent casein.
‡A complete diet containing 20 per cent gluten as sole source of protein.

TABLE V. EFFECT OF DIETARY PROTEIN ON SUSCEPTIBILITY TO INFECTION

PROTEIN (PER CENT)	AVERAGE WEIGHT CHANGE	NUMBER OF MICE	CUMULATIVE DEATHS AT INDICATED DAYS POSTINFECTION			
			7	14	21	28
Casein 15*	+3.0	9	0	0	1	8
Casein 5†	+0.1	10	3	4	9	10
Gluten 15‡	+0.8	10	1	4	8	9
Mixed plant 15§	+3.8	10	0	3	4	5

Animals maintained on diets for 10 days before infection with 0.05 ml. *Myco. fortuitum* in vivo.
*A complete diet containing 15 per cent casein.
†A complete diet containing 5 per cent casein.
‡A complete diet containing 15 per cent gluten as sole source of protein.
§A mixture of rice and soy bean flour which has an amino acid pattern similar to that of 15 per cent casein.

In all published studies of the effect exerted by protein intake on resistance to infection, it has been the practice to keep the animals on the

experimental diets throughout the period of experimentation. We have repeatedly observed, however, that even very short periods of depletion may be sufficient to increase susceptibility. One particular example will suffice to illustrate this statement.

Mice were fed a complete diet (Sherman type) consisting of 33 per cent whole milk, 66 per cent whole wheat, and one per cent NaCl. They were all infected with 0.1 ml. of a virulent culture of bovine tubercle bacilli by the intravenous route. They were then divided into two groups. For one of these groups, the Sherman diet was replaced by a diet free of protein but otherwise complete on the fifth and sixth days and again on the twelfth and thirteenth days. In each group the disease was allowed to follow its course in 12 of the animals and the time of death was recorded. The other animals (15 per group) were sacrificed 9, 12, and 19 days after infection, and a quantitative bacteriologic study was made of the number of tubercle bacilli in their spleens. The results of this experiment are summarized in Table VI.

TABLE VI. EFFECT OF TRANSIENT NUTRITIONAL DISTURBANCES ON MOUSE TUBERCULOSIS

	CUMULATIVE DEATHS AT INDICATED TIMES (WEEKS) AFTER INFECTION				NUMBER OF TUBERCLE BACILLI IN SPLEEN AT INDICATED TIMES (DAYS) AFTER INFECTION		
Sherman diet*	4	6	8	10	9	12	19
Uninterrupted diet	0	0	0	6‡	7†	10	170
Replaced by protein-free diet on days 5, 6, 12, and 13	2‡	3	6	11	25	100	340

*A mixture of 66 per cent whole wheat, 33 per cent whole milk, and 1 per cent NaCl.
†Average of 5 mice: to be multiplied by 2×10^3 to give total number of colonies recovered per organ. Infection 0.2×10^{-6} ml. intravenously.
‡Out of 12 mice infected in vivo with 0.01 ml. of bovine tubercle bacilli.

As appears from the results presented in Table VI, replacement of the Sherman diet by a protein-free diet for two days on two consecutive weeks during the course of the tuberculous process decreased the survival time of the animals in a dramatic manner. Many other experiments, not to be reported here, have confirmed that transient nutritional disturbances can alter profoundly the resistance of animals to infection.

EFFECT OF THE NUTRITIONAL STATE ON TOXINEMIA

In all the experiments reported so far, the survival time of infected animals was used as criterion of the nutritional effect. At first it was assumed that increase in survival time was an expression of the fact that the bacteria were destroyed more effectively or multiplied more slowly in the organs of animals receiving the proper diets. In order to test this hypothesis, animals on various experimental diets were sacrificed at short intervals of time after infection and quantitative bacteriologic studies were made of the numbers of microorganisms that could be recovered from their organs. Contrary to expectation, it was found that whatever the diet used and whatever its effect on survival time the numbers of bacteria recovered from blood, liver, lung, spleen, and kidney were

essentially the same in all animals during the 48 hours that followed infection.[36] On the basis of these facts, it seems unlikely that the poor diets exerted their resistance-depressing effects by interfering with the clearing power of the organs or by favoring the multiplication of the pathogens, at least during the first two days after infection.

To account for the shorter survival time of the animals on the inadequate diets, we are now postulating that these animals are less resistant to the toxic manifestations resulting from the presence of the bacteria or bacterial products in their organs. Although a few preliminary experiments have given results compatible with this hypothesis, the findings are still too limited to warrant dogmatic statements at this time. It is sufficient to outline briefly one single experiment that bears on this point.

Three groups of mice were placed on experimental diets for 6 days. One group received a complete diet containing 20 per cent casein; the other received the same diet but with only 5 per cent casein; the third was fed only corn grain. Diets and water were given ad lib. All mice received by the intravenous route 0.5 ml. of a culture of nonvirulent (coagulase negative) staphylococci (isolated from the air) in admixture with bacterial endotoxin (derived from *Serratia marcescens*).

TABLE VII. DIET AND SUSCEPTIBILITY OF MICE TO TOXICITY OF COAGULASE NEGATIVE STAPHYLOCOCCI

DIET	AVERAGE WEIGHT CHANGE (GM.)	NUMBER OF MICE	CUMULATIVE DEATHS AT INDICATED HOURS POSTINFECTION			
			6	9	12	24
20 C*	+3.2	10	0	0	0	1
5 C†	−2.2	10	2	4	6	6
Whole corn‡	−2.5	10	2	3	4	7

Animals were maintained on diets for 6 days, then infected with cells from 0.5 ml. air staphylococcus resuspended in 0.2 ml. of glucose solution containing 0.1 mg. endotoxin (from *Serratia marcescens*).

*A complete diet containing 20 per cent casein.

†A complete diet containing 5 per cent casein.

‡Corn was the only component of diet (water ad lib.).

The results presented in Table VII reveal that mice fed a diet low in protein (5 per cent casein) or deficient in several factors (corn) for 6 days proved highly susceptible to nonvirulent coagulase-negative staphylococci when these organisms were administered in association with bacterial endotoxin. Under the same conditions, most animals fed 20 per cent casein survived. The rapidity with which death ensued in the susceptible animals (less than 2 hours in some cases) strongly suggests that the lethal outcome was due more to the effect of the bacterial toxins than to bacterial multiplication.[36]

EFFECT OF DIETARY FACTORS ON TISSUE RESPONSE

To a very large extent the course of infectious processes is determined by the immunologic and histologic responses to the presence of infectious agents and their products. In this respect, the first mechanism that comes to mind to account for the

infection-enhancing effect of malnutrition is that protective antibodies are less readily formed or more rapidly lost in malnourished individuals. Indeed, antibody depletion has been repeatedly demonstrated with diets deficient either in amino acids, pantothenic acid, pyridoxine, or pteroyl glutamic acid.[2, 5, 44, 51] It appears, however, that the serum levels of antibodies are appreciably lowered only in the case of profound deficiencies, rarely encountered under natural conditions.[3, 39] It is true that, as recently shown, depletion of serum protein and negative nitrogen balance can be brought about very rapidly by feeding amino acid antagonists to experimental animals[54]; but despite its great theoretical interest, this finding is not likely to have its counterpart in nature. In fact, interference with production or loss of antibody can hardly be considered as a common expression of dietary disturbance. However, it must be emphasized that failure to develop immunity can probably occur through mechanisms other than those resulting in impairment of antibody production. For example, suggestive evidence has been presented that the type of fatty acid in the diet can influence the development of antitubercuious immunity in mice.[15]

The effect of the nutritional state on the inflammatory reaction and on the histologic tissue response appears of more direct relevance to ordinary infectious processes. While as yet little can be said concerning the effect of dietary factors on inflammation, it is obvious that the walling-off reaction, involving as it does the deposition of acidic polysaccharides and of fibrous proteins (fibrin and collagen), imposes great synthetic demands on the infected organism. Although the detailed steps of this reaction are not yet well understood, it is known that the synthesis of mucopolysaccharides and of collagen is greatly retarded when the diet is deficient in ascorbic acid or in certain amino acids, particularly lysine and the sulfur amino acids.[1, 8, 10, 11, 30, 34, 46, 53] In the light of these facts there might be some justification, after all, in regarding ascorbic acid as an "anti-infectious" vitamin. Lysine also deserves some further emphasis since this amino acid is an absolute requirement for the synthesis of β hydroxylysine which is one of the essential constituents of collagen.[45] Thus, it is worth considering the possibility that plant proteins which are deficient in lysine fail to afford resistance to infection because they are not adequate for collagen synthesis. Witness, for example, the failure of tuberculous patients to develop a productive tissue response when fed diets deficient in "animal" proteins. Unquestionably, the nutritional state also affects susceptibility to infection through many indirect channels. For example, it is known that acute starvation can activate the pituitary-adrenal cortical system, whereas chronic undernutrition decreases adrenal activity. In view of the important role played by pituitary and adrenal hormones in infectious processes, it can be surmised that some of the effects associated with acute starvation and chronic undernutrition[6, 23, 35, 48] may be the result of disturbances in hormone activity.

PROTECTIVE EFFECTS OF NUTRITIONAL DEFICIENCIES

All the examples quoted so far have been selected to illustrate that resistance is decreased when the intake of certain nutrients is low. It must be recognized, however, that resistance can also be decreased by the addition of certain foodstuffs. Thus, enrichment of the diet with seed oils and particularly with wheat-germ oil aggravates mouse salmonellosis and tuberculosis.[36, 39]

Even more striking is the fact that nutritional *deficiencies* can increase resistance to infection. For example, riboflavin deficiency in chicks decreases the severity of *Plasmodium lophurae* infections,[42] and ascorbic acid deficiency in monkeys represses the multiplication of *Plasmodium knowlesi*.[24] Monkeys and rats do not develop malaria as long as they are fed a diet lacking para-amino-benzoic acid (paba) because this vitamin is required for the multiplication of the plasmodium.[14] There is some evidence, furthermore, that the same situation applies to human beings and that it accounts for the fact that African children exposed to malaria remain free of the disease as long as they are breast fed (milk does not contain paba).

It has been repeatedly observed that limitation of food intake or deficiencies in essential growth factors (various vitamins and amino acids) retard the progress or change altogether the character of several types of viral infection.[9, 13, 21, 31, 49] Likewise, in tissue cultures the viruses remain dormant as long as the infected cells are maintained in deficient culture media.[28] It appears that certain nutritional deficiencies prevent infected cells from carrying on the synthetic processes needed for viral replication. This fact may account for the clinical experience that virus diseases often exhibit a less acute character in patients who are underfed or malnourished than in well-fed persons.

A most intriguing illustration of the fact that lack of certain dietary factors can exert a protective effect has come recently from investigations on allergic encephalomyelitis.[41] It has been found that mice fed a diet consisting of whole wheat and whole milk are more likely to develop this disease than mice fed a semisynthetic diet made up of highly purified constituents. Susceptibility to the disease can be increased by adding certain dietary factors to the semisynthetic diet. In other words, one should not overlook the possibility that deleterious responses to the phenomena and products of infection can be enhanced or even brought about by certain dietary constituents.

DISCUSSION

It can be assumed a priori that the course of infectious processes is affected by the nutritional state through many different mechanisms involving both the activities of the parasite and the response of the host to their presence. Information scattered through the literature (not all quoted here) provides experimental evidence for an effect of nutrition on (1) the rate of multiplication and destruction of the pathogens in vivo; (2) the production of toxins by the pathogens; (3) the histochemical characters of the lesions in the host;

(4) the rate and effectiveness of his immunologic response; (5) his susceptibility to the various manifestations of toxemia. Other aspects of the inter-relationship between nutrition and infection will unquestionably come to light, but what is known is already sufficient to make clear that the effects of dietary factors on infectious processes are extremely diverse.

There is even evidence that a dietary factor which increases resistance under certain conditions can become deleterious under other circumstances. In fact, actual situations illustrating this paradoxical possibility are easy to imagine. Thus, a dietary factor capable of increasing antibody production and thereby of exerting a protective effect could conceivably intensify potentially dangerous allergic phenomena. Deficiencies in vitamins or in amino acids capable of lowering resistance to *bacterial* infections can increase resistance to certain *viral* diseases by depriving host cells of factors essential for replication of the viruses. Furthermore, one given nutritional factor can either aggravate or repress a viral infection depending upon the circumstances, as has been shown with pyridoxine and pneumonia virus of mice and with protein and influenza virus.[21, 27, 49]

These complexities may well account for some of the controversies regarding the effects that dietary constituents exert on infection. In addition, there is little doubt that deficiencies in essential amino acids are more likely to promote infection in young individuals during periods of rapid growth than in adults who have reached a semisteady state. Physiologic or traumatic accidents leading to stress or tissue repair also may correspond to periods during which deficiencies become more critical. This is probably of particular importance with reference to surgical interventions.[33] The regularity and rapidity with which diets inadequate in protein have been found to increase susceptibility to bacterial infections in the experiments reported above may stem in part from the fact that the tests were carried out with young animals (within 1 to 4 weeks after weaning). It is also relevant to this problem that the infection-enhancing effect of the deficiencies could be rendered more acute by submitting the animals to an additional stress: namely, the injection of bacterial lipopolysaccharides (endotoxins) at the time of infection. As these lipopolysaccharides cause a pathologic state which has similarities with traumatic shock, one may postulate that the nutritional status is of particular importance in determining susceptibility to infection at the time of trauma.

The protein reserves of the body deserve emphasis since they probably influence the rate at which susceptibility to infection increases when the amino acid intake is inadequate. As is well known, the plasma protein level remains remarkably constant under a wide range of conditions. However, in order to maintain this normal plasma level, the body must call on homeostatic mechanisms which mobilize the proteins normally stored in large amounts in the lymph, extracellular fluid, and other reserves.[29, 50, 55] It is probable, therefore, that the potential deleterious effects of amino acid deficiencies are brought

out more readily and more rapidly when these protein reserves are low than when they are abundant. In other words, the past nutritional history of the individual as well as the anabolic demands at the time of observation must be kept in mind when one attempts to define the nutritional requirements which are optimal for resistance to infection. The same parameters also influence the length of time that elapses before the deficiency manifests itself in the form of decreased resistance. Related to these facts is the finding that, in mice at least, the breakdown in resistance caused by nutritional deficiencies is rapidly reversible.[7, 35] This rapid reversibility may be of practical importance, since it bids fair to lead to procedures for the control of the nutritional status at critical times. It may be of interest to recall here that tuberculous patients whose disease had become acute in prisoners' camps often recovered rapidly when placed under adequate nutritional conditions at the end of the war.

Repeatedly during this paper we have emphasized that the diets most effective in assuring rapid growth of noninfected animals are not necessarily the ones that give greatest resistance to infection.[4, 7, 18] In other words, the ability to confer resistance is a criterion different from those usually considered by nutritionists. More generally stated, this view implies that nutritional requirements must be defined not only in terms of the needs of the normal individual in a steady state but also with regard to the necessity of meeting additional demands imposed by the states of stress (an expression overworked, but usefully vague for the present purpose). Infectious diseases constitute "stresses," each with its own particular characteristics. For this reason, it can be expected that several types of additional criteria will be required to define the nutritional state optimum for each type of infection.

CONCLUSIONS

The nutritional state can affect infectious processes through many unrelated mechanisms, modifying either the multiplication and activities of infectious agents, the susceptibility of the host to their toxic manifestations, or the immunologic and histochemical response to infection.

There is even evidence that a given dietary factor can be beneficial in some circumstances, indifferent in others, or deleterious in still others, depending upon the type of infectious process under consideration as well as the genetic constitution, age, past history, and physiologic state of the infected individual.

The effect of a given dietary factor on infection cannot be predicted from its effect on the growth rate of the uninfected host. In fact, resistance to infection, as to other forms of stress, may be highest under nutritional conditions which do not favor growth. The ability to resist infections and their associated stresses is the expression of nutritional criteria different from, and supplementary to, those usually considered by nutritionists.

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SEVERE HYPERCHLOREMIC ACIDOSIS OF UNUSUAL ETIOLOGY

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HYPERCHLOREMIC acidosis is commonly associated with renal tubular disease, with administration of inhibitors of renal carbonic anhydrase, or with diarrhea. It has also been described in some patients who have undergone transplantation of the ureters to the colon, but the extent of the contribution of renal and extrarenal factors to the pathogenesis of the acidosis in these patients is disputed.

This paper presents studies of an unusual situation which resembles that observed in patients with ureterosigmoidostomies but in which the acidosis seemed entirely attributable to extrarenal factors.

CASE REPORT

The patient was a white boy who was first admitted to the North Carolina Memorial Hospital on Nov. 8, 1955, at 6½ years of age for corrective surgery for an imperforate anus. The history revealed that the child had undergone unsuccessful surgery for this anomaly on the second day of life. At 2 weeks of age, a double-barreled colostomy had been performed, after which he passed normal-appearing fecal material via the proximal stoma. Allegedly, the patient voided no urine for the first 2 weeks of life, but after the colostomy had been established, virtually all of the urine was voided via the distal colostomy stoma. Following a series of urethral dilatations at the age of 3 months, some urine was voided through the urethra, although most of it still was voided from the colostomy.

The child's diet had always been adequate, although he consistently preferred liquids to solids. For at least 2 years prior to admission he had consumed large quantities of fluid, as much as 4 quarts per day. Supplemental multivitamins providing 400 I.U. of vitamin D per day had been given since birth. Abdominal distention had been present since early life, and the patient had required frequent enemas. In the 3 years prior to admission he had had multiple episodes which occurred about monthly and which were characterized by anorexia, vomiting, and labored deep respiration. These episodes were self-limited and usually lasted one to two days; the symptoms were sometimes thought to be improved by a soapsuds enema instilled into the proximal colostomy loop.

The patient's growth and development had been slow. He sat alone at 1 year of age and walked with support at 2 years; he had never walked alone. However, he was able to ride a tricycle without apparent difficulty. Eruption of the deciduous teeth was delayed and no permanent teeth had appeared.

The patient was first seen in the outpatient department on Aug. 4, 1955. At that time, because of the dangers of large tap-water enemas,[1] daily saline enemas were advised in

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order to begin preparation of the bowel for surgery. These were administered for 2 weeks prior to admission.

Physical examination on admission to the hospital revealed a small, pale, poorly nourished child with a markedly protuberant abdomen. His weight and height were 31 pounds and 37 inches, respectively, each in the third percentile for his age group. The temperature, pulse, respiration, and blood pressure were all normal. The head appeared large (circumference, 53.5 cm.) in proportion to the rest of the body. There was slight frontal bossing. Ten maxillary and 10 mandibular deciduous teeth were present and were markedly carious. There was slight enlargement of the costochondral junctions. The heart and lungs were normal except for a blowing "functional" cardiac murmur. The abdomen was markedly distended and fecal masses were palpable throughout the colon. There was a stricture of the proximal colostomy stoma which barely admitted the tip of the examining finger. The anus was imperforate, although there was evidence of some external sphincter function. The genitalia and the neurologic examination were normal.

Laboratory studies on admission revealed the concentration of hemoglobin to be 12.8 Gm. per 100 ml.; the white blood cell count was 9,000 per cubic millimeter, with a normal differential. Urine obtained from the distal colostomy stoma showed a specific gravity of 1.008; pH, 6.8; protein, 1+; there were no reducing substances or ketones. The urinary sediment contained 3 to 4 white cells per high-power field. Examination of the stool for trypsin was normal. Roentgenograms of the abdomen revealed a markedly gas- and fecal-filled colon. Instillation of contrast medium into the distal loop of the colostomy demonstrated that it was markedly distended, and deep introduction of methylene blue into it was almost immediately followed by appearance of the dye in urine voided via the urethra. An intravenous pyelogram showed that the dye was well concentrated by the left kidney but none was demonstrated in the right kidney. The left kidney showed some degree of hydronephrosis. The skeletal age was markedly retarded.

Course.—During the second night in the hospital, the patient vomited several times. On the morning of the third day (November 10), he was semicomatose, slightly dehydrated, and in marked respiratory distress, with deep, rapid respirations. Chemical determinations at this time (see Table I and Fig. 1) revealed a severe hyperchloremic acidosis associated with hypokalemia. Therapy was begun with an intravenous infusion containing 45 mM. of sodium bicarbonate. This was followed by another infusion of 10 mM. of potassium chloride in glucose and water. Following these infusions, the condition of the patient was somewhat improved: he was more alert, but there was no marked change in the degree of the hyperpnea. Subsequent chemical determinations made during and after this infusion (Table I) demonstrated slight increases in the total carbon dioxide content and in the concentration of potassium in the serum.

At this time, a review of the history and the chemical data suggested that the pathogenesis of the metabolic abnormalities involved the following factors in varying degrees: (1) the loss of bicarbonate and potassium ions and the gain of chloride ions due to the passage of most of the urine through the distal loop of the colon; (2) similar losses and gains secondary to the large saline enemas which had been given in the proximal loop of the colostomy for the previous two weeks; (3) some degree of renal tubular insufficiency. The first possibility was examined by comparing the composition of the urine obtained from the distal colostomy with that obtained simultaneously from the urethra. The colostomy urine showed

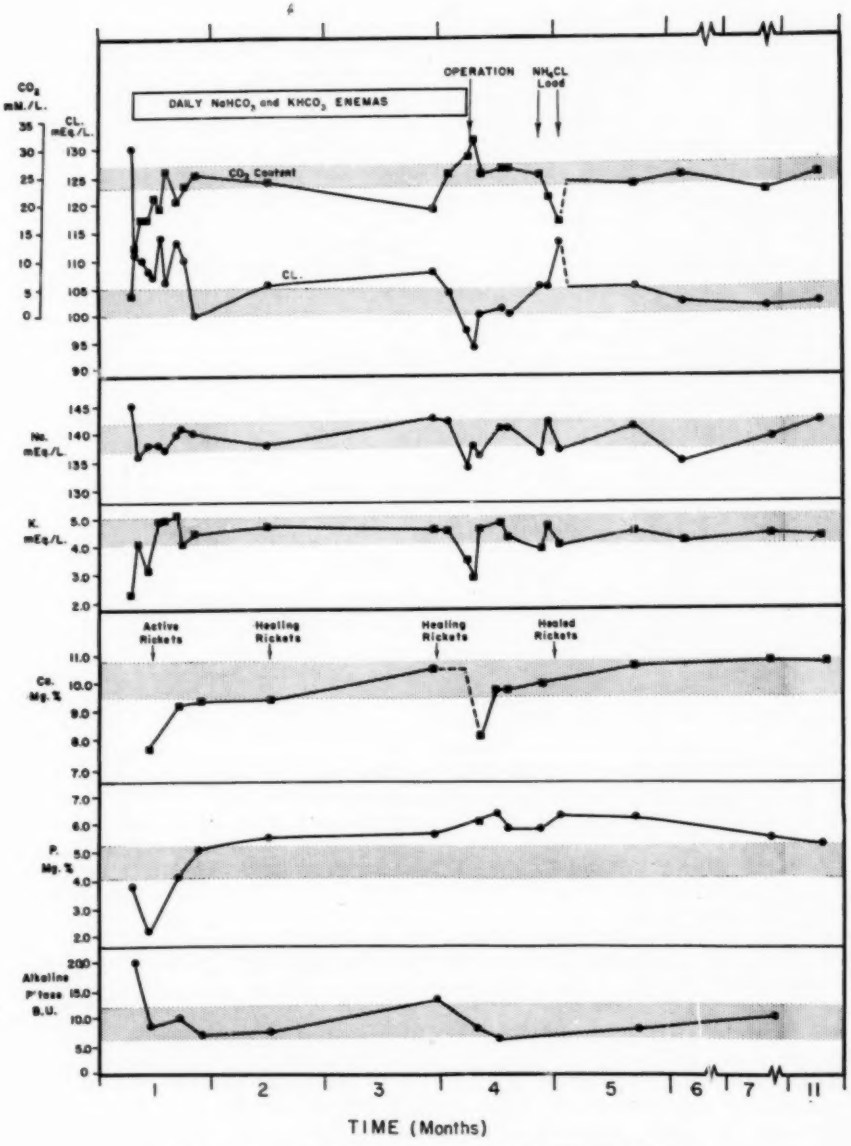

Fig. 1.—Chemical data obtained during the patient's course.

TABLE I. RESULTS OF CHEMICAL DETERMINATIONS

DATE	SODIUM (MILLIEQUIVALENTS PER LITER)	POTASSIUM (MILLIEQUIVALENTS PER LITER)	CHLORIDE (MILLIEQUIVALENTS PER LITER)	CO_2 CONTENT (MILLIMOLS PER LITER)	BLOOD pH (–37° C.)	UREA—NITROGEN (MILLIGRAMS PER 100 ML.)	TOTAL PROTEIN (GRAMS PER LITER)	TOTAL CALCIUM (MILLIGRAMS PER 100 ML.)	INORGANIC PHOSPHORUS (MILLIGRAMS PER 100 ML.)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	COMMENT
Nov. 10 1955	145	2.3	130	3.8		31	6.6		3.8	19.7	Blood glucose was 70 mg. per cent
Nov. 10 1955				7.3*	6.95*						During $NaHCO_3$ infusion
Nov. 10 1955	133	3.6	115	5.5*	7.18*	33					Before enema
Nov. 10 1955	136	4.1	111	12.1*	7.31*						After enema
Nov. 11 1955	141	3.5	115	13.7*	7.33*						Before enema
Nov. 11 1955	140		110	17.4*	7.34*						After enema
Nov. 12 1955	138	3.1	108	17.3*	7.36*	19					Before enema
Nov. 12 1955	140		107	21.6*	7.38*						After enema
Nov. 14 1955	137	4.7				13	5.0	7.6	2.2	8.6	Active rickets by x-ray
Nov. 15 1955	138	4.9	114	19.6*	7.34*	19					
Nov. 18 1955	137	4.9	106	26.3		11					
Nov. 21 1955	140	5.1	113	20.5		17	5.7	9.2	4.1	10.0	
Nov. 23 1955	141	4.1	110	23.4		13					
Nov. 25 1955	140	4.4	100	25.5		15	5.8	9.3	5.1	7.2	
Dec. 13 1955	138	4.7	106	24.0		17	5.8	9.3	5.5	7.4	Healing rickets by x-ray
Jan. 30 1956	143	4.6	108	19.4		20	6.3	10.5	5.6	13.1	No enema for previous 2 days
Feb. 2 1956	142	4.5	104	25.5		18					Healing rickets by x-ray
Feb. 8 1956	134	3.5	97	28.1		16					
Feb. 9 1956	138	2.9	94	31.2		14		8.0		8.0	Third postoperative day
Feb. 10 1956	136	4.6	100	24.6		9					
Feb. 16 1956	141	4.8	101	26.6		12	6.3	9.7	6.3	6.1	
Feb. 18 1956	141	4.3	100	26.2		12	6.3	9.7	5.8		
Feb. 27 1956	136	3.9	105	24.1		14	5.8	9.9			Begin NH_4Cl load
Feb. 29 1956	142	4.7	108	21.5		19					
March 2 1956	136	4.0	113	16.5		18	6.8		6.3		End NH_4Cl load
Range	135-142	4.2-4.5	101-105	21.5-25.0		13-18	6.7-7.3	10.6-10.7	5.2-6.3	7.9-11.6	Multiple subsequent determinations

All determinations performed in duplicate by methods previously reported from this laboratory.[9, 10]
*Arterial blood.

a pH of 7.0, and the value of the sum of the concentrations of sodium and potassium minus that of chloride, which is an approximate measure of the concentration of bicarbonate, was 31 mEq. per liter. On the other hand, the urine voided by way of the urethra had a pH of 5.0; the value of sodium and potassium minus chloride was (–) 27 mEq. per liter. This value represents the approximate concentration of ammonium ion in the urine. These findings suggested that the acidosis was due principally to alterations of the urine as it passed through the colon rather than to intrinsic renal tubular disease.

Accordingly, it was thought that the acidosis might be treated by instillation of sodium bicarbonate solutions in the proximal colostomy loop in the hope that bicarbonate ions would be exchanged for chloride ions, thereby raising the concentration of the former while decreasing the concentration of the latter in the extracellular fluid. Hence, 1,500 ml. of a solution containing 140 mM. of sodium bicarbonate and 4 mM. of potassium chloride were introduced into the proximal loop in aliquots of 100 to 200 ml. Each aliquot was withdrawn after a period of 15 to 30 minutes, the whole procedure occupying about 3 hours. The entire volume of fluid was recovered and subsequent analysis showed a net removal of 27 mEq. of chloride and 19 mEq. of potassium from the patient; no net removal of sodium occurred. Chemical studies of the serum just before and again one hour following the procedure are shown in Table I and revealed that the serum chloride fell from 115 to 111 mEq. per liter while the total carbon dioxide content rose from 5.5 to 12.1 mM. per liter. The whole blood pH rose concomitantly from 7.18 to 7.33. The child's condition was further improved following the enema.

By the following morning (November 11), there had been only a slight further rise in the total carbon dioxide content (Table I). A second enema was then given, with results similar to those of the previous day. Thereafter, these enemas were given daily with either 1.0 or 1.5 L. of a solution containing 140 mM. of sodium bicarbonate and 10 to 15 mM. of potassium bicarbonate per liter. On each of 5 occasions when measurements of the composition of the fluid were made, there was a net removal of from 15 to 30 mEq. of chloride but little or no net removal of cations. With this measure, in addition to frequent aspirations of urine from the distal loop, the total carbon dioxide content remained normal or nearly normal throughout the remainder of the hospitalization, despite the intake of a normal hospital diet with an estimated content of about 3 Gm. of sodium chloride per day. It should be noted in evaluating the data in Table I that from November 15 on the determinations were made before the daily bicarbonate enema had been given.

Initial studies of the concentrations of total calcium, inorganic phosphorus, and alkaline phosphatase in the serum revealed chemical evidence of rickets (Table I). Roentgenograms of the wrists and knees showed moderately severe rickets. Therapy for rickets was aimed primarily at the correction of the acidosis by the methods outlined above; therapeutic doses of vitamin D were not given. With control of the acidosis, the levels of inorganic phosphorus and alkaline phosphatase in the serum returned to normal or near-normal values (Fig. 1).

In view of the considerable improvement which had occurred during the short period of time in the hospital, corrective surgery was temporarily postponed in the hope of further improving the child's general condition and of healing the rickets. Accordingly, the patient was discharged from the hospital on November 27 on the following therapeutic

program: (1) daily enemas with sodium and potassium bicarbonate solution; (2) frequent aspiration of urine from the distal loop; (3) a normal diet with an estimated content of 3 Gm. of sodium chloride per day.

Two weeks following discharge, the patient was seen in the outpatient department. There had been a gain in weight of 1½ pounds and improvement in his general condition. Studies of the serum electrolytes revealed normal values (Table I). Roentgenograms showed considerable healing of the rachitic process.

The patient was readmitted to the hospital on Jan. 30, 1956. In the interval he had continued to thrive and showed an additional 2 pounds gain in weight. Two weeks prior to admission he had walked alone for the first time. The laboratory data on this admission showed a mild hyperchloremic acidosis which was attributed to the fact that he had not received any bicarbonate enemas for the previous 2 days. Following reinstitution of this measure, normal values for total carbon dioxide content and chloride in the serum were again attained.

With general anesthesia, the patient underwent surgery. The distal loop was found to be a large, dilated, thin-walled sac which terminated deep in the pelvis in a fistula connected to the posterior urethra. The fistula was divided and the colostomy site and much of the distal loop were resected. Continuity of the colon was established by an end-to-end anastomosis; a pull-through procedure was then performed with a mucocutaneous anastomosis at the anus. The right kidney was not palpable; the left felt normal in size, although the ureter was enlarged.

The postoperative course was complicated by 2 seizures on the second postoperative day which began on the left side of the face but rapidly became generalized. Each was associated with an unexplained fever. Chemical studies on the following morning (February 9) revealed hypocalcemia, hypokalemia, and metabolic alkalosis; no supplemental potassium had been administered in the parenteral fluids. Potassium depletion was treated with supplemental potassium, and on the following morning normal values for total carbon dioxide and potassium were obtained. The seizures did not recur and the remainder of convalescence was uneventful.

During the latter part of convalescence, renal function was tested in an effort to determine the degree to which intrinsic renal disease could have contributed to the original acidosis. The rate of glomerular filtration (clearance of inulin) was normal, the mean of 5 periods of 20 minutes each was 46 ml. per minute (128 ml. per 1.73 mm.^{2} per minute). The excretion of phenolsulfonphthalein was 20 per cent in 15 minutes and 75 per cent in 120 minutes. With hydropenia for 12 hours, the specific gravity of the urine rose to 1.022. The ability to acidify the urine was tested by loading with ammonium chloride (75 mM. per day; 279 mM. per 1.73 mm.^{2} per day). On the fourth day of loading, the urinary ammonia increased from the control value of 9.7 to 52.0 mM. per day while the titratable acid increased from 9.9 to 29.9 mEq. per day. During loading, the total carbon dioxide content of the serum fell from the initial value of 24.1 to 16.5 mM. per liter, while the serum chloride rose from 105 to 113 mEq. per liter (see Table I). When the urinary data are normalized to 1.73 mm.^{2}, they are comparable to those seen in normal adult subjects given a comparable load.

The patient has been followed for a period of 32 months since his operation. In repeated chemical studies no abnormalities have been detected (Table I). The patient has had several bouts of acute pyelonephritis, perhaps secondary to a urethral stricture. Complete fecal

continence has not been achieved, although there is a partial control. The patient has been troubled by chronic constipation and fecal impactions. Among other remedies, large saline enemas have been administered, but in no instance has any evidence of recurrence of hyperchloremic acidosis been detected. Since the operation, the patient has shown an accelerated gain in weight; at 9 years of age his weight was in the twenty-fifth percentile. His increase in stature, however, was not proportionately accelerated, his height at this time being just below the third percentile for his age group.

DISCUSSION

The pathogenesis of the metabolic abnormalities exhibited by this patient, consisting of hyperchloremic acidosis, potassium depletion, and rickets, can be reconstructed in most details from the data presented. The evidence suggests that the urine leaving the kidney was appropriate in composition considering the existence of the acidosis. Since most of the urine was routed through the large distal loop, further important changes in composition occurred. These consisted of reabsorption of chloride ions and excretion of bicarbonate and potassium ions, changes similar to those recorded by D'Agostino and co-workers[2] following instillation of sodium chloride solutions into the colon of the dog. As a result of these mechanisms, the final urine voided from the body consisted of a dilute alkaline fluid containing appreciable amounts of bicarbonate and potassium ions but relatively poor in chloride.

In many respects our patient resembles those with ureterosigmoid anastomoses, some of whom develop hyperchloremic acidosis and potassium depletion. In this latter group the relative importance of renal and extrarenal factors in the development of the acidosis is disputed.[3-6] Our patient presented the unique opportunity to evaluate the renal factor separately following correction of the anatomic abnormality. The results of these studies suggest that the acidosis was entirely due to extrarenal factors, since no abnormalities were found in the ability of the kidney to acidify the urine.

It seems likely that some degree of acidosis had been present since early life. In fact, the multiple episodes of hyperventilation which the patient had had prior to admission may have represented clinically recognizable bouts of metabolic acidosis. The presence of rickets in this patient in spite of adequate prophylaxis also speaks for long standing acidosis. The large saline enemas which had been given prior to admission probably constituted an additional factor conditioning the severity of the acidosis which occurred during the first hospitalization, since this measure would lead to additional losses of bicarbonate ions.

Although the association of chronic renal tubular acidosis and rickets is well known, the mechanisms underlying the development of the bone disease are not clear. Albright and Reifenstein[7] suggested that parathyroid hyperplasia incident to losses of calcium in the urine was primarily responsible for the hypophosphatemia and, hence, for the rickets. On the other hand, Harrison[8] has recently

suggested that acidosis may inhibit the normal action of vitamin D upon the renal tubular reabsorption of phosphorus, thereby leading to hypophosphatemia and to rickets. Regardless of the mechanism, it is well established that correction of the acidosis and not vitamin D therapy is of primary importance in the treatment of rickets associated with this type of acidosis. The data on the patient reported here are entirely consistent with this observation.

SUMMARY

The occurrence of severe hyperchloremic acidosis associated with depletion of potassium and with rickets in a child with an imperforate anus and a rectourethral fistula is reported. Data are presented suggesting that the primary cause of the acidosis was the loss of bicarbonate ions as the result of a change in the composition of the urine as it passed through the colon. Following reparative surgery, the ability of the patient to acidify the urine in response to ammonium chloride was normal. These considerations strongly suggest that the pathogenesis of the acidosis was entirely extrarenal.

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HYPERBILIRUBINEMIA IN PREMATURE INFANTS

A Follow-Up Study

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EVIDENCE that kernicterus is directly related to hyperbilirubinemia has been accumulating in recent years. Hsia, Allen, Gellis, and Diamond[1] demonstrated such a causal relationship in their patients with erythroblastosis, and Zuelzer and Mudgett[2] observed a similar association in patients whose hyperbilirubinemia had been caused by diseases not related to isoimmunization.

The next problem of interest to us was the study of premature infants with "physiologic jaundice" to determine whether high levels of bilirubin occurring in these otherwise "normal" infants had any influence on the development of kernicterus.

We had the opportunity to study 100 premature infants who developed wide ranges of serum bilirubin levels, some reaching heights which would not have been permitted in the therapeutic regimen of today. The clinical condition of these infants was observed closely during the first few weeks of life and a follow-up study of 49 of the group was made from 2 to 3 years later for the detection of clinical evidence of kernicterus.

PROCEDURES

In 1953, one of us (M. S. D.) made serial determinations of the serum bilirubin of 100 consecutive premature infants. Only total bilirubin measurements, by the method of Hsia, Hsia, and Gellis,[4] were made and it was assumed that unless there was associated parenchymal liver disease any elevations which took place were due to increased amounts of indirect bilirubin. None of the infants had apparent or proved sepsis and all patients with demonstrable isoimmunization were excluded from the series.

Many of these infants had received 10 mg. of vitamin K daily for 3 or 4 days as a part of the routine procedure being used in the nursery at that time. In the light of our present knowledge these doses were large and may have had some influence in producing high bilirubin levels. Bound and Telfer[5] have since shown that an excessive dose of vitamin K given to premature infants can be a factor in the production of hyperbilirubinemia, and Lucey and Dolan[6] have shown that large amounts of the vitamin administered intravenously to mothers during labor can also produce hyperbilirubinemia and kernicterus in the premature infant.

Each infant was examined immediately after birth and given a rating of "good," "fair," or "poor" based upon such factors as color, cry, muscle tone, respiration, and cardiac rate. Clinical evidence of kernicterus was looked for among the infants who developed

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hyperbilirubinemia. One exchange transfusion had been performed because of the suspicion of a B-O incompatibility which later proved to be unfounded.

Autopsies were performed on all of the 8 infants who died during their hospital stay and special examination was made for evidence of kernicterus.

All of the parents of the 92 infants discharged from the premature nursery were asked to return their children for examination in 1955 to 1956, by which time these infants had reached ages of 2 or 3 years. The group of 42 who appeared were examined by us in respect to their neuromuscular status.

No specific intelligence tests were attempted at this time. Minor deviations from normal which are difficult to interpret at these ages were ignored so that the children who were rated as abnormal in this study were obviously so.

An additional 7 patients, of the original 92, had attended clinics in this vicinity during the first year of life and their charts contained sufficient data for evaluation of their neuromuscular development. They have been included in the study.

RESULTS

Of the original group of 100 infants, 8 died during the neonatal period and 2 of these were found to have kernicterus at autopsy. These 2 patients had had serum bilirubin levels of above 20 mg. per 100 ml., while the other 6 infants with no evidence of kernicterus had had levels of less than 20 mg. per 100 ml.

Of the 49 surviving infants who could be followed when they were 1 or more years of age, 5 (10.2 per cent) were found to have neuromuscular abnormalities suggestive of kernicterus. The influence of neonatal levels, of serum bilirubin, the birth weights of the patients, and their general condition during the first days of life have been summarized in the following tables.

TABLE I. NEUROMUSCULAR ABNORMALITIES AS RELATED TO SERUM BILIRUBIN LEVEL

MAXIMUM SERUM BILIRUBIN LEVEL	NUMBER OF INFANTS	ABNORMAL INFANTS	
		NUMBER	PER CENT
0 to 20 mg. per 100 ml.	31	0	0
20 to 30 mg. per 100 ml.	14	2	14.3
30 to 40 mg. per 100 ml.	4	3	75
Totals	49	5	10.2

TABLE II. NEUROMUSCULAR ABNORMALITIES AS RELATED TO BIRTH WEIGHT

BIRTH WEIGHT (GRAMS)	NUMBER OF INFANTS	ABNORMAL INFANTS	
		NUMBER	PER CENT
Under 1,000	2	0	0
1,000 to 1,500	11	3	27.3
1,500 to 2,000	16	2	12.5
2,000 to 2,500	20	0	0
Totals	49	5	10.2

Relationship of Neuromuscular Abnormalities to the Serum Bilirubin Levels in the Neonatal Period.—No

neuromuscular disorders suggestive of kernicterus developed in the patients whose serum bilirubin levels were less than 20 mg. per 100 ml. (Table I). However, the incidence rose sharply as the serum bilirubin levels rose. Of the 4 infants who had had levels in the range of from 30 to 40 mg. per 100 ml. There is, of course, a tendency for infants of low birth weights to have higher than average serum bilirubin levels and this has been substantiated in our series (Table III).

The Relationship of Neurologic Abnormalities to the Condition of the Infant at Birth.—The birth condition

TABLE III. SERUM BILIRUBIN AS RELATED TO BIRTH WEIGHT

MAXIMUM SERUM BILIRUBIN LEVEL	BIRTH WEIGHT (GRAMS)				TOTALS
	500 TO 1,000	1,000 TO 1,500	1,500 TO 2,000	2,000 TO 2,500	
0 to 20 mg. per 100 ml.		4	11	16	31
20 to 30 mg. per 100 ml.	2	5 (2)	3	4	14
30 to 40 mg. per 100 ml.		2 (1)	2 (2)		4
Totals	2	11 (3)	16 (2)	20	49
Per cent over 20 mg.	100	64	32	20	

Figures in parentheses represent affected infants.

TABLE IV. NEUROMUSCULAR ABNORMALITIES AS RELATED TO THE CONDITION OF THE INFANT AT BIRTH

CONDITION AT BIRTH	NUMBER OF INFANTS	ABNORMAL INFANTS	
		NUMBER	PER CENT
Poor	8	1	12.5
Fair	11	3	27.0
Good	30	1	3.0
Totals	49	5	10.2

TABLE V. NEUROMUSCULAR ABNORMALITIES AS RELATED TO SERUM BILIRUBIN LEVELS AND CONDITION AT BIRTH

MAXIMUM SERUM BILIRUBIN LEVEL	CONDITION AT BIRTH			TOTALS
	POOR	FAIR	GOOD	
0 to 20 mg. per 100 ml.	5	3	23	31
20 to 30 mg. per 100 ml.	1	7 (2)	6	14
30 to 40 mg. per 100 ml.	2 (1)	1 (1)	1 (1)	4
Totals	8 (1)	11 (3)	30 (1)	49

Figures in parentheses represent affected infants.

during the first few days of life, 3 developed symptoms and signs of kernicterus.

The Relationship of Neurologic Abnormalities to Birth Weight.—All of the patients with abnormalities suggestive of kernicterus were very small at birth, the heaviest of the 5 patients weighing 1,636 grams (Table II). of 3 infants who developed signs of kernicterus had been rated as fair, with one in each of the other two categories, so that there was no definite trend to indicate that the infants in the poorest condition at birth were most likely to develop abnormal neuromuscular signs (Table IV). Likewise, there was no trend for the infants

whose conditions were rated as poor at birth to develop higher serum bilirubin levels than those considered to be in good condition (Table V).

A pair of twins included in this survey provide an interesting illustration of the predominant influence of hyperbilirubinemia. L. T. 1 was a colored girl who weighed 1,636 grams at birth and her condition was rated as fair. She was placed in a Bloxsom airlock for several hours and then transferred to an incubator with oxygen. At 10 hours of age the lungs were well aerated and respirations were normal. She developed a serum bilirubin level of 38.7 mg. per 100 ml. and in later life had neuromuscular abnormalities suggestive of kernicterus. The twin, L. T. 2, was a boy who weighed 2,028 grams at birth and whose condition at birth was also rated as fair. He had marked retractions of the chest and diminished breath sounds bilaterally. Intratracheal aspiration was performed and he was placed in a Bloxsom airlock for several hours and then transferred to an incubator with oxygen. He had respiratory difficulties until 48 hours of age. His bilirubin level never rose above 19.6 mg. per 100 ml. In spite of his greater degree of respiratory difficulty following birth, he did not develop any neuromuscular abnormalities during the next 2 years.

Detailed Account of the Five Infants Who Developed Neuromuscular Abnormalities.—As mentioned above, one of these 5 infants, D. B., received an exchange transfusion on the assumption that he had a B-O blood type incompatibility. This was subsequently proved to be a false diagnosis (Table VI). The oxygen received by these infants for a period of from 16 to 31 days was a "weaning" procedure. It was designed, in accordance with a theory prevalent at that time, to prevent retrolental fibroplasia and did not necessarily reflect cyanosis or respiratory distress.

Most important was the absence of signs of neuromuscular disorder that could be construed as evidence of kernicterus in the early weeks of life. These patients were kept under close observation and although such signs as lethargy and episodes of cyanosis were reported, they did not occur more frequently in the affected infants than in the others. No abnormalities of the neuromuscular system could be detected.

DISCUSSION

We shall probably never have another opportunity to study a group of premature infants with such high levels of serum bilirubin. In recent years decreases in the dosage of vitamin K have been associated with a reduction in the incidence of hyperbilirubinemia. If it is evident that indirect bilirubin levels of the serum will exceed 20 mg. per 100 ml., irrespective of the cause, exchange transfusions are now instituted and repeated whenever necessary to prevent the development of dangerous degrees of hyperbilirubinemia.

Our observations point strongly to the probability that a high level of bilirubin is the most important etiologic factor producing kernicterus. Whether some of the factors which lead to hyperbilirubinemia in the early days of life make the brain unusually receptive to the toxic influences of bilirubin is a problem not yet solved. Such abnormalities as immaturity of the liver,[9] immaturity of other organs,

TABLE VI. DETAILS CONCERNING ABNORMAL INFANTS

PATIENT	MAXIMUM BILIRUBIN	BIRTH WEIGHT (GRAMS)	BLOOD GROUPS Rh TYPES VITAMIN K DOSAGES	CONDITION AT BIRTH AND IN IMMEDIATE NEONATAL PERIOD	SUBSEQUENT COURSE IN HOSPITAL	CONDITION ON DISCHARGE FROM HOSPITAL	NEUROMUSCULAR STATUS
D. B. C-F	31.6 mg. per 100 ml.	1,620	infant O+ mother B+ vitamin K, 10 mg. daily for 3 days	"Poor" Gasping respirations. Placed in airlock. All right at 48 hours of age. Mother a diabetic	Exchange transfusion at height of bilirubin. At this time infant was vigorous and active and took feedings well. Oxygen for 17 days	No abnormalities	At 2 years of age: could not sit or hold head erect; spastic and athetoid; mentally retarded
M. E. C-M	20.7 mg. per 100 ml.	1,304	infant B+ mother B+ vitamin K, 2.5 mg. daily for 4 days	"Fair" Placed in airlock initially. Transferred to Isolette at 6 hours of age. Respiratory difficulty for 3 days	Lethargic until the eleventh day and during period of jaundice. Oxygen for 31 days	No abnormalities	At 2 years of age: could not walk or sit; spastic paraplegia; mentally retarded
D. H. W-M	30.0 mg. per 100 ml.	1,474	infant O– mother O– vitamin K, 5 mg. daily for 3 days	"Good" Cesarean section. Developed rapid shallow respirations. All right on the fourth day	Regurgitation. Cyanotic episodes. Very lethargic for 4 days while jaundiced. Oxygen for 20 days	No abnormalities except retrolental fibroplasia	At 3 years of age: mentally retarded; athetoid; no retrolental fibroplasia
V. H. C-F	20.0 mg. per 100 ml.	1,332	infant A+ mother A+ vitamin K, 10 mg. daily for 4 days	"Fair" Moderate cyanosis. Respirations fairly regular. All right 24 hours later	Uneventful. Active and took feedings well during period of jaundice. Oxygen for 16 days	No abnormalities. Fundi of both eyes were normal at 3 weeks of age	Chart examined: in clinic when child 13 months old. Diagnosed as mentally retarded and athetoid. Exotropia of right eye with retinal scar. Could not sit alone at 1 year of age
L. T. C-F	38.7 mg. per 100 ml.	1,636	mother O+ infant O+ vitamin K, 5 mg. daily for 4 days	"Fair" Marked cyanosis. Placed in airlock, then in Isolette. Improved rapidly in the first 24 hours	Condition good at 24 hours of age. At height of bilirubin, remained active and took feedings well. Oxygen for 16 days	No abnormalities	At 2 years of age: reflexes hyperactive; not spastic; walked with a wide-base gait; nystagmus and strabismus; deaf

hypoxia,[17] defects in the enzyme system of the liver which conjugates indirect bilirubin with glucuronic acid,[10] toxic effects of drugs,[5, 11-13] or increases in the permeability of the blood-brain barrier have been mentioned as causes of hyperbilirubinemia and kernicterus and will not be discussed in detail here.

An important conclusion reached from our observations was the difficulty in making the diagnosis of kernicterus in the first weeks of life. Vaughn, Allen, and Diamond[7] have stated that all infants with kernicterus show definite signs of the disorder during the neonatal period, but Jones and his co-workers[8] found a significant number of children with brain damage who had exhibited no signs or equivocal signs during the newborn period.

Perlstein[15] stated that older children with kernicterus usually have athetosis, auditory disturbances, defects of the ocular movements, and hypoplasia of the enamel of the deciduous teeth. Lamm and Koven[16] have been impressed by the occurrence of deafness and athetosis, occasionally accompanied by spasticity.

The behavior of the 5 abnormal infants of our study did not differ typically from that of other premature infants in the nursery at the time. Both groups included infants who had periods of listlessness and episodes of apnea and regurgitation which may or may not have been indications of brain damage. None of the affected patients had convulsions or other signs of hyperirritability. Three of the abnormal infants, including the 2 with the highest levels of bilirubin, were vigorous, active, and took their feedings well at the height of the bilirubinemia.

When they had reached ages of 1 or more years, the abnormal infants exhibited signs which were unmistakably evidence of brain damage.

It is planned to study again as many as possible of the 92 surviving premature infants when they are 6 to 7 years of age. They will then be in school and should be easier to locate. Complete mental and physical examinations will be performed, including audiometric studies. Electroencephalograms will be obtained when indicated. It is expected that in this survey the percentage of abnormal children will be greater than the percentage found in this series.

SUMMARY

Serial determinations of serum bilirubin were made during the first week of life of 100 premature infants. None of these patients had any demonstrable evidence of infection or isoimmunization. Those who developed hyperbilirubinemia were considered to have "physiologic jaundice" and at that time (1953) no treatment was instituted.

Eight infants died, 2 of whom had kernicterus. Their bilirubin levels had been greater than 20 mg. per 100 ml. The remaining 6, who died of other causes, had levels below 20.

Of the surviving infants, none had neuromuscular abnormalities on discharge from the nursery. Of a group of 49 patients examined when they were 1 year or more of age, 5 had neuromuscular abnormalities highly suggestive of kernicterus. All of these patients had had serum bilirubin levels of more than 20 mg. per 100 ml. during the neonatal period.

The relationship of kernicterus to factors of birth weight and condition

of the patients at birth was not so distinct and clear-cut as the relationship to hyperbilirubinemia.

The difficulty of making a clinical diagnosis of kernicterus in the first weeks of life was emphasized and makes the observation of patients for a number of years to detect the true incidence of the disease essential.

Exchange transfusions are indicated for all infants with hyperbilirubinemia in the newborn period if it is evident that the serum bilirubin levels will exceed 20 mg. per 100 ml.

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HEME PIGMENT AND BILIRUBIN REBOUND FOLLOWING EXCHANGE TRANSFUSION IN INFANTS WITH ERYTHROBLASTOSIS FETALIS

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CHAPEL HILL, N. C.

IN accordance with suggestions of Mollison and Cutbush[1, 2] and Hsia and co-workers[3] concerning the relation between serum bilirubin level and occurrence of kernicterus, the policy has been established of performing exchange transfusions in infants with erythroblastosis fetalis in order to maintain the level of bilirubin in serum below 20 mg. per cent. That exchange transfusion lowers the incidence of kernicterus has been amply demonstrated. It has been assumed that this procedure, by removing bilirubin, eliminates the toxic effect of this agent upon cells of the central nervous system. Bilirubin inhibits oxidative phosphorylation in isolated rat-liver and rat-brain mitochondria, with a depression of cellular respiration as a concomitant phenomenon.[4] Mesobilirubin and hematin are similarly toxic in rat-diaphragm and rat-brain homogenates.[5]

Following exchange transfusion in jaundiced newborn infants, a "rebound" increase of bilirubin in serum is frequently noted. An important factor in the rebound is the variable extravascular reservoir of bilirubin which may diffuse in or out of plasma. Variations in age, hepatic function, time elapse during exchange procedure, amount of blood used, and presence or absence of a continued hemolytic process constitute a major difficulty in predicting height and duration of the rebound phenomenon. Heme pigments might also be expected to occupy a variable extravascular reservoir, to diffuse in and out of plasma, and to share in the rebound phenomenon.

This study was undertaken to characterize spectrophotometrically the absorption patterns of bilirubin and heme pigments in serum before and after repeated exchange transfusions; to compare clearance of bilirubin and heme pigments from serum by exchange transfusion; and to assess the extravascular reservoir and gradient between this space and plasma of bilirubin and, if present, of heme pigments. The results would be expected to support criteria for initial and repeated exchange transfusions.

METHODS

Infants who met diagnostic criteria for erythroblastosis fetalis were used. Early jaundice, hepatosplenomegaly, pallor, edema, a hemoglobin concentration of less than 15 Gm. per cent, a maternal Rh titer higher than 1:64 during pregnancy, and a positive direct Coombs test were clinical and

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laboratory guides for diagnosis. Exchange transfusion was performed on infants under the age of 5 days with a serum bilirubin level of 20 mg. per cent or higher and on infants with more than a minimal degree of jaundice before 24 hours of age. Each was diluted 1:50 in normal saline. Optical density was measured in these samples from 350 μ to 500 μ at 5 and 10 μ increments and at 576 μ and 622 μ. Maximal absorption of heme pigments occurs at 410 to 415 μ and of bilirubin at 470 μ.

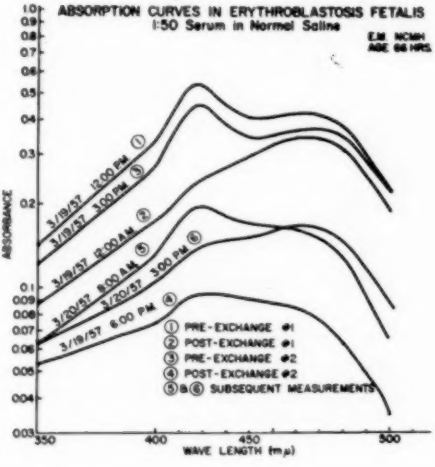

Fig. 1.

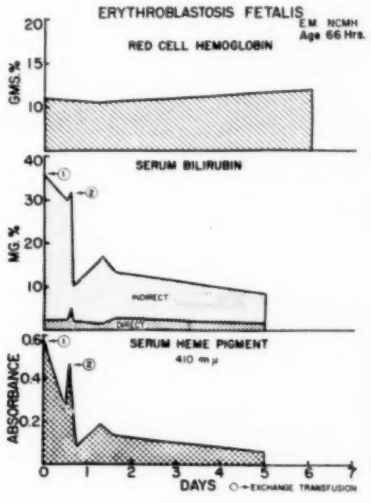

Fig. 2.

Fig. 1.—Heme pigment and bilirubin spectrophotometric absorption in an infant with erythroblastosis fetalis before and after two exchange transfusions.

Fig. 2.—Heme pigment and bilirubin levels in patient's serum before and after two exchange transfusions (same subject as in Fig. 1).

exchange amounted to 500 ml. of whole blood; elapsed time was 1 to 1½ hours for the exchanges. Hemoglobin measurements were made by the cyanmethemoglobin method, using a Bausch & Lomb Spectronic 20 photoelectric colorimeter. Bilirubin determinations were made using the van den Bergh diazo reaction at 1 and 30 minutes for direct and indirect components. Spectrophotometric analyses were done on a Beckman DU spectrophotometer. Blood was carefully collected to avoid hemolysis. After centrifugation at 2,000 r.p.m. for 15 minutes, the serum

RESULTS

Spectrophotometric absorption patterns before and after two exchange transfusions in an erythroblastotic infant at 66 hours of age are shown in Fig. 1. Peaks at 410 μ and 470 μ representing heme pigments and bilirubin, respectively, are clearly demonstrable. Fig. 2 illustrates that the hemoglobin values in the same subject did not change appreciably while bilirubin, measured by the van den Bergh reaction, dropped only slightly following the first exchange. On the other hand, heme pigment decreased sharply

and subsequently rebounded. The effect of the second exchange was much more pronounced, with only a slight rebound in levels of bilirubin and heme pigments.

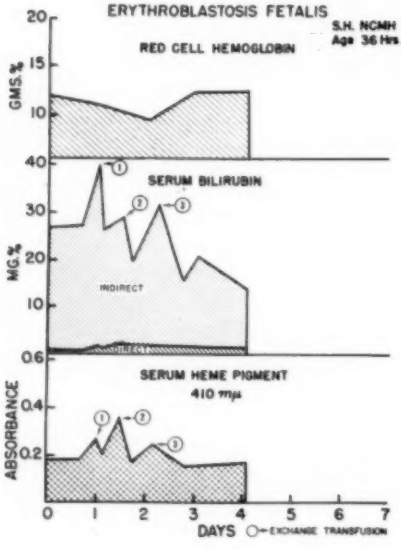

Fig. 3.

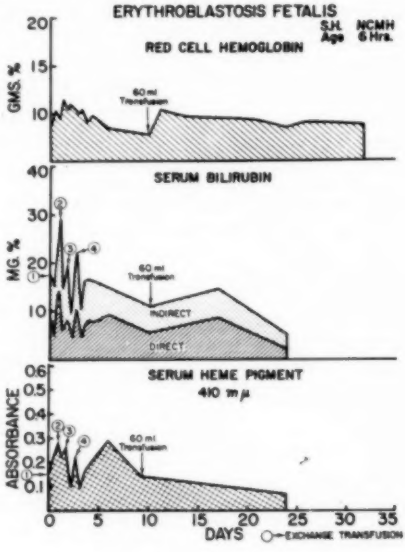

Fig. 4.

Fig. 3.—Heme pigment and bilirubin levels in infant's serum before and after three exchange transfusions.

Fig. 4.—Heme pigment and bilirubin levels in patient's serum before and after four exchange transfusions and one direct transfusion.

The course over 4 days of an infant subjected to three exchange transfusions is shown in Fig. 3. The rebounds of both bilirubin and heme pigments were striking. In Fig. 4 are shown the effects of four exchange transfusions on bilirubin and heme pigments levels in the serum of an infant whose blood was first exchanged at 6 hours of age.

Absorption of bilirubin at 410 μ should be considered in evaluating the quantity of heme pigments from the spectral curves. Bilirubin concentrations of 20 to 40 mg. per cent contributed approximately 0.1 to 0.2 optical density unit at this wave length. At concentrations less than 20 mg. per cent, absorption at 410 μ was less than 0.1 optical density unit.

DISCUSSION

Exchange transfusions are performed chiefly for the purpose of removing vulnerable sensitized red cells, thereby decreasing potential bilirubin formation from accelerated hemoglobin breakdown. Approximately 85 per cent of the infant's original sensitized red cells are usually removed by the first exchange. Anemia is not significant except in those cases undergoing three or more exchanges. The direct removal of bilirubin appears to be the major if not the sole purpose of a second, third, or fourth exchange

transfusion when bilirubin does not remain at a sufficiently low level after the first exchange.

The explanation of the bilirubin rebound phenomenon apparently depends upon existence of a variable extravascular reservoir. In this study the rate of increase of serum bilirubin after four exchanges is as rapid, or as a rule more rapid, than the rate of accumulation of serum bilirubin from birth to the first exchange transfusion. There is little doubt that residual and newly formed erythrocytes may account for some reaccumulation of bilirubin and heme pigments, but in those cases undergoing one or two exchange transfusions, formation of these substances from red cells is negligible.[6] Since both heme pigments and bilirubin are bound to plasma protein, the extravascular distribution and rebound of these substances are probably determined to a great degree by the available protein-binding sites supplied by transfused plasma. One must hypothesize that a gradient for bilirubin from the tissues to the plasma is established, and since the change of heme pigments in serum closely parallels that of bilirubin after exchange transfusion, it would appear that a similar gradient exists for both components.

The components of the 410 to 415 μ absorption peak have not been identified. It has been suggested that these pigments may be heme-protein complexes such as methemalbumin or heme-containing enzymes such as catalase or peroxidases.[7, 8] Hematin and mesobilirubin may also contribute to the 410 to 415 μ absorption peak.

The mechanism by which bilirubin or other heme pigments inhibits respiration of brain and other cells is unknown. A possible explanation is that the activity of certain respiratory enzymes in the brain depends upon the prosthetic heme group, and the deleterious effects of hyperbilirubinemia might be the result of competition between bilirubin and heme for complex formation with the protein moiety of the enzymes. Since the pigment observed histologically in the brain of patients with kernicterus has not been identified with certainty, mechanisms for production of the disorder must remain speculative until the pathogenesis is more clearly demonstrable.

SUMMARY AND CONCLUSIONS

Clearance of bilirubin and heme pigments from serum by exchange transfusion is related to persistence following transfusions of substantial amounts of these substances in the tissues. This study demonstrates a rapid and variable rise of bilirubin and heme pigments in serum of erythroblastotic infants following exchange transfusions. The rise presumably results from establishment of new equilibria in distribution of bilirubin and heme pigments between the extravascular space and plasma. The factors determining the distribution, movement, and pathologic effects of these compounds are poorly understood.

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Infants Dying From Suffocation by Plastic Material

Dr. Harold Jacobziner, Assistant Commissioner of Health, New York City, has called attention to recently reported deaths of infants and young children from suffocation by the thin plastic bags used for wrapping clothes after dry cleaning and the like. This material is frequently used as sheet covers and is often given to children to play with. According to newspaper reports, an electrostatic charge is generated on the thin plastic by friction from handling and it consequently clings to the face of the child.

In peering through this material the child is apt to have it literally grab him by electrical attraction to his face. If this happens, only the prompt intervention of an adult will prevent tragedy.

Some children, according to newspaper reports, have died as a result of putting the plastic bags over their heads and being suffocated.

In view of the widespread use of the plastic in the home physicians are requested to alert parents to the reported existing hazards and to warn them not to give these plastic materials to children as playthings.

From the City of New York Department of Health.

CONGENITAL LEUKEMIA

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LEUKEMIA is not an uncommon disease of infants and children. The incidence in the 0- to 4-year-old range is estimated at 5 per 100,000[1] and the over-all incidence at 1 per 15,000.[2] However, since acute leukemia in the newborn infant is extremely rare, this case is presented not only because of its comparative rarity but also because of its dramatic appearance and the unexpected sudden death of the infant. There have been 2 reviews of the subject in American literature, one in 1944[3] and another in 1957,[4] in each of which the authors cite 20 cases from the literature and adds 2 of his own. The foreign literature contains several excellent reviews of the subject[5-9] in addition to a rather complete presentation of the subject by Schiavini.[10] The first cases were recorded in 1918: one in a 1-month-old infant reported by Tancré[11] and another by Holsclaw[11a] in an 11-month-old infant. Since this time, there have been isolated case reports.[6-9, 12-29]

The newborn infant may present many symptoms characteristic of leukemia. There may be nodular skin infiltrations and hemorrhagic manifestations of the skin and mucous membrane including petechia, purpuric spots, ecchymosis, and hematoma. A hemorrhagic tendency may also be evident with gingival bleeding, epistaxis, hematemesis, and melena. Bleeding from the urethral meatus has also been described.[26] The liver and spleen are usually enlarged to variable degrees, with or without generalized adenopathy. Temperature elevation, jaundice, abdominal distention, listlessness, and gross edema are other findings. Pallor is frequently present, although not in all instances nor to the degree one might expect, since the life of the red blood cell varies from 40 to 200 days, with an average of 110 to 130 days.[30] Thus, the erythrophthisic effect of the leukemic process has not had time to show its full effect in the newborn infant.

At autopsy one finds extensive leukemic infiltration of all the organs. The white blood count in these cases can vary from 3,200 to 1,600,000 per cubic millimeter.[5] Of all the cases reviewed, only one case, other than this one, had 1,500,000 or more white blood cells per cubic millimeter.[18]

CASE REPORT

The patient, a boy, was born at the Astoria General Hospital on June 11, 1958, after an apparently normal pregnancy and delivery to an Rh positive, group A mother. The birth weight was 7 pounds, 6 ounces. The mother is white and was 31 years of age at term. In 1947 a subtotal gastrectomy, jejunojejunostomy, and

gastrojejunostomy were done on her because of a mass which was attached to the stomach. The histologic diagnosis of this mass was teratomatous cyst with embryonal sarcoma with invasion of the stomach. In March, 1957, she was admitted to a hospital ing an esophagram, chest plate, and barium enema. In August, 1957, 5 months after exposure to diagnostic x-radiation, she had her last menstrual period which began her pregnancy.

The infant gained weight normally and when seen by his physician on

Fig. 1

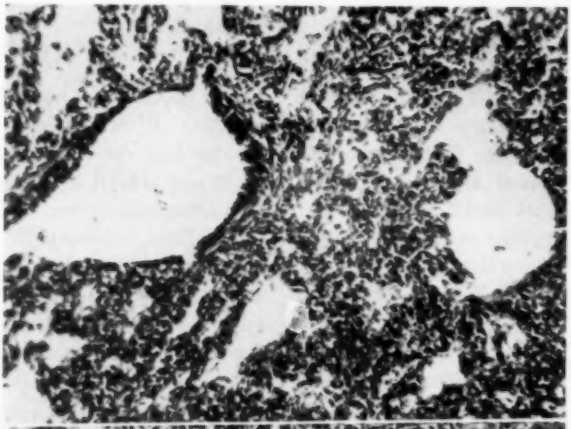

Fig. 2.

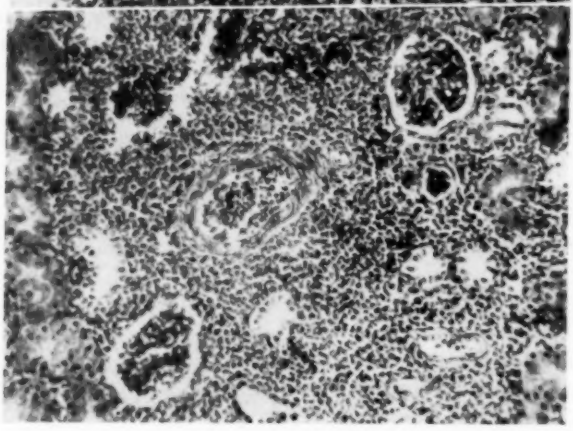

Fig. 1.—Lung. Marked edema and interstitial infiltration by leukemic cells.
Fig. 2.—Kidney. Almost all of the normal kidney structures are absent, being replaced by leukemic cells.

because of gastrointestinal bleeding due to a marginal ulcer at the gastrojejunal site. A second gastrojejunostomy was done. No other pathologic changes were found at surgery. During this last hospitalization she had a gastrointestinal x-ray series includ- June 25, 1958, his weight was 8 pounds and 12 ounces. The infant was seen again on July 2, 1958. The examination did not disclose any abnormality and the mother offered no complaints. On the morning of July 9, the infant refused his feeding for

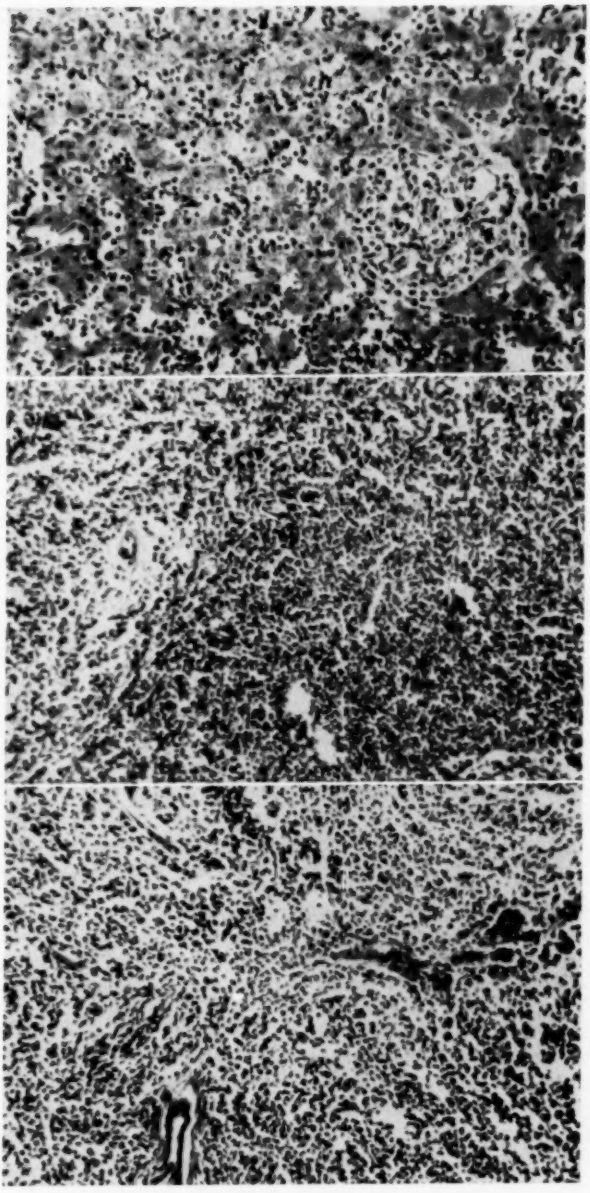

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3.—Liver. Marked parenchymatous degeneration with diffuse leukemic infiltration which is more concentrated in the portal triads.

Fig. 4.—Spleen. Complete loss of architecture. Some sections are replaced by leukemic cells.

Fig. 5.—Pancreas. Marked diffuse leukemic cell infiltration with complete loss of architecture.

the first time. Later that same morning the mother thought that the child "did not look well." The infant was examined in the early afternoon at the home; he appeared quite ill, with an ashen-gray appearance and shallow respirations. The liver and spleen were markedly enlarged. The skin was mottled. The infant was admitted to the Astoria General Hospital. He died 2 hours after admission despite oxygen and other supportive treatment. A blood count obtained before death revealed: red blood cell count, 3,140,000; hemoglobin, 6.85 Gm.; white blood cell count, 1,500,000. Examination of the peripheral smear showed that the white cells outnumber the red cells in each field. The cells were essentially the same, with only slight variation in size. The leukemic cell was represented by a large nucleus with even chromatin of a light staining nature and minimal cytoplasm. Nucleoli were present but indistinct. Some smudge cells were present. There was an occasional nucleated red cell; fewer leucocytes and cells showing mitosis were found.

Postmortem Examination.—The lungs (each 40 grams) were studded with an enormous number of hemorrhagic spots. The mediastinal lymph nodes were multiple and enlarged and the mesenteric lymph nodes were enlarged and white in color. The liver (300 grams) was smooth and had a slight icteric tinge but was otherwise whitish yellow in color. The spleen (75 grams) had a pyoid-gray appearance and the capsule was tense. The kidneys (each 20 grams) had a whitened cortex and a slightly darker medulla. Fetal lobulations were present and some hemorrhages noted. Adrenals showed marked thinning of the cortex. The stomach was markedly enlarged, infiltrated, and white in color. It had lost its normal architecture. The pancreas was large and white. The blood was black with a putty-like consistency.

Microscopic Examination.—It revealed the following: The lungs (Fig. 1) showed marked edema and there was pronounced interstitial cellular infiltration by leukemic cells, with some leukemic pneumonic consolidation. Almost all of the normal structures of the kidney (Fig. 2) were absent and replaced by leukemic cells. Minimal tubular and glomerular elements were present. The liver (Fig. 3) showed marked parenchymatous degeneration and marked leukemic infiltration, diffuse in nature and more concentrated in the portal triads. The spleen (Fig. 4) revealed complete loss of architecture with entire sections almost completely replaced by leukemic cells. Mature lymphatic cells were absent and true germinal follicles were not seen. The heart showed the vascular channels filled with leukemic cells which in some areas infiltrated into the muscle bundles and in some areas the capillaries were outlined by packed leukemic cells. The lymph nodes showed complete loss of architecture and were made up entirely of leukemic cells. The stomach, large bowel, and small bowel showed marked leukemic infiltration, particularly in Peyer's patches. The adrenals revealed lipoid depletion and the vessels were filled with leukemic cells. There was marked diffuse leukemic cell infiltration in the pancreas (Fig. 5), with complete loss of architecture. Only an occasional pancreatic gland was seen.

DISCUSSION

This case can be considered as congenital stem-cell leukemia. Whether the cells belonged to the lymphoid or myeloid series is extremely difficult to say. Since they were so immature that differentiation was practically impossible.[31] Cifarelli[32] dwells particularly on the confusion in literature in trying to establish hematologic distinctions of these immature cells.

He prefers to use the term nongranulous or leukoblast since this term can be applied to leukemic cells of either the myeloid or lymphoid series.

The clinical criteria necessary to establish a diagnosis of congenital leukemia should include the following[7]: (1) inconsistency of anemia (The anemia is isochromic and never hypochromic and may not be severe because of the expected life of the red blood cells as noted above); (2) thrombocytopenia; (3) abnormal cells in the peripheral blood; (4) symptoms present either at or within a few days of birth; (5) enlargement of the liver, spleen, and lymph nodes; (6) absence of anything in the history to indicate syphilis or erythroblastosis fetalis.

The pathologic criteria should include the following[15]: (1) more infiltration of the organs than could plausibly have occurred since birth; (2) infiltration with early cell forms; (3) infiltration of nonhemopoietic centers as well as of the liver, spleen, and lymph nodes.

An interesting finding is the association of congenital leukemia with mongolism.[7, 22, 26, 28, 29, 33, 34] Whether this association is purely fortuitous or based on a common etiologic agent is highly speculative. Schunk and Lehman[22] have noted that granulocytes are first seen during the seventh embryologic week and lymphoblasts during the eighth week. The hematopoietic system is undergoing critical maturation at the time developmental disturbances resulting in mongolism are most likely to occur. An intrauterine viral infection has been suggested[4] as a possible common etiologic agent. The association of mongolism with duodenal atresia also occurs more frequently than one would expect by chance, and a common etiologic agent has also been suggested for this pair of anomalies[35]; but this assumption was questioned by Brescia and Quinn.[36] Leukemia in the newborn infant, as could be expected, is also associated with many other congenital anomalies.[24, 29]

A leukemic mother has not been known to give birth to a leukemic child,[37] although a case of leukemia was reported in a 9-month-old infant whose mother was leukemic.[40]

The influence of x-radiation in the etiology of leukemia of the newborn infant is undergoing careful scrutiny. The mother of our case had diagnostic radiation 5 months prior to the beginning of gestation. Whether or not this was a factor is a moot point. It has been shown, for example, that leukemia occurs nine times more frequently in radiologists than in nonradiologist doctors.[38] Ionizing radiation has a definite influence on the incidence of leukemia. The incidence of leukemia is high (1:80) at distances close to the hypocenter of an atomic explosion (0 to 999 meters) and approaches a normal incidence 2,500 meters or more from the hypocenter.[2] A marked increase has been reported in the incidence of leukemia and other types of neoplasms in children during the first 10 years of life when their mothers received diagnostic roentgenographic examinations during pregnancy.[39] Whether or not x-radiation received prior to pregnancy is an etiologic factor requires further study and observation.

SUMMARY

We have presented a case of congenital stem-cell leukemia in an infant 28 days of age. The infant was apparently well until the twenty-eighth day of life when he refused his feedings, rapidly deteriorated, and died in a matter of a few hours.

The white blood count was extremely elevated, 1,500,000 per cubic millimeter, and all the organs, hemopoietic as well as nonhemopoietic, were markedly infiltrated with leukemic cells.

A review of the literature is presented.

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ACUTE LEUKEMIA TREATED BY IRRADIATION AND MARROW TRANSPLANT

A Case Report Emphasizing Metabolic Imbalance

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THE effects of ordinarily lethal irradiation have been successfully overcome in rodents,[1] canines,[2] and primates[3] by the use of intravenous infusions of cellular suspensions of donor marrow. This repopulation of the marrow in animals immediately suggests a parallel use in human beings who have received lethal irradiation or whose marrow has been otherwise damaged with resultant agranulocytosis or aplastic anemia. Another interesting application would be the treatment of generalized malignancies such as leukemia which are radiosensitive. Theoretically, the irradiation would destroy the malignant cells and the marrow transplant would counteract the irradiation.

This paper records our experience with a 4-year-old boy with acute stem-cell leukemia, who, after all conventional methods of treatment had failed, was given lethal total body irradiation followed by intravenous administration of donor marrow. The radiation, hematologic, and metabolic complications are felt worthy of documentation.

CASE REPORT

J. B., a $3\frac{11}{12}$-year-old white boy, was first seen at the University of Arkansas Medical Center on May 3, 1957. For 3 months he had had pain in the lower extremities, loss of appetite, and was easily bruised. After bone marrow aspiration, he had been diagnosed elsewhere as having acute lymphatic leukemia.

Physical examination found him to be well developed and well nourished, with a soft systolic murmur, a liver enlarged 5 cm. below the mid-clavicular line, and numerous scattered ecchymoses and petechiae. The right elbow and wrist were swollen, tender, and hot.

Clinical Course.—During May, the fourth month of illness, this patient had a partial remission on therapy with amethopterin, 2.5 mg. daily, which lasted 4 weeks; this was followed by a complete remission during July, coincident with the administration of 80 U. of ACTH gel daily for 10 days. He was then maintained on 37.5 mg. of 6-mercaptopurine for $2\frac{1}{2}$ months and was clinically well and hematologically free of abnormal cells. Following this remission, his marrow and peripheral blood again showed many blast cells and few platelets (Table I). No hematologic response was obtained from 80 U. of ACTH gel for 14 days or from prednisone (100 mg. daily by mouth) and amethopterin (2.5 mg. daily for 21 days). He continued to have marked anemia, petechiae, bone pain, and swelling of the joints.

At this time, irradiation and marrow transplant were decided upon. In preparation the child was isolated on

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the ward and given aureomycin prophylactically for 3 days prior to irradiation. On November 13, 1957, he received cobalt 60 gamma irradiation, with an effective whole body dose of 700 r. After irradiation he looked sallow and his cardiac rate rose as did his respiratory rate, which was accompanied by an expiratory grunt. Hydrocortisone sodium succinate (10 mg. in 5 per cent dextrose solution), intravenously, was begun but tachycardia (150 to 160 per minute), tachypnea (40 to 50 per minute), and hypertension (120 to 130/80 to 90) continued. Arrhythmias noticed 4 hours after irradiation disappeared following fluid therapy (Table II). Thirty-six hours postirradiation the patient was given 5.8 billion donor marrow cells in 125 c.c. of the donor's plasma intravenously. There was no reaction. On the third postirradiation day marked oliguria was present. He was cystoscoped, and the right ureter and kidney pelvis were irrigated with bicarbonate solution. The left ureteral orifice could not be visualized. Despite intravenous sodium bicarbonate (11 mEq. per kilogram of body weight per day) he became more acidotic and oliguric. No evidence of marrow regeneration was observed. The patient died the morning of the fifth postirradiation day.

Laboratory and Roentgenographic Studies.—The pattern of the blood picture throughout the illness is shown in Table I. Bone marrow examinations revealed stem-cell replacement on May 6 and June 19, 1957. The bone marrow differential on July 12, 1957, was normal except for erythroid hyperplasia, but it again showed blast cell replacement on September 20 and remained blastic until the end of the final admission. Before irradiation all urinalyses were normal as were radiographs of the skull, chest, and long bones.

The hemoglobin just prior to irradiation was 12.3 Gm. per cent, but it dropped to 7.0 Gm. per cent two days later. During this same period the leukocyte count fell from 7,800 to 350 cells per cubic millimeter, while the platelet count dropped from 27,000 to 20,000 per cubic millimeter.

The day after irradiation the urine showed a pH of 4.5, 3+ proteinuria, and 20 to 80 erythrocytes per high-power field in a noncentrifuged specimen. The urinary sodium at this time was 40 mEq. per liter, and the urinary potassium, 102 mEq. per liter.

Serum electrolyte values following irradiation showed an elevation of serum potassium, phosphorus, uric acid, and nonprotein nitrogen and a lowering of pH, sodium, calcium, CO_2 combining power, and chloride (see Table II).

An enlarged right kidney shadow was noted radiographically on the day following irradiation and again on the third postirradiation day.

Serial electrocardiograms during this postirradiation period showed supraventricular tachycardia, S-T segment depression, and the T wave changes suggestive of hyperkalemia. In addition, there were prolonged S-T and Q-T segments, suggesting hypocalcemia.

Autopsy Report.—Grossly there were numerous ecchymotic areas of the skin. Four hundred milliliters of blood-tinged fluid were found in the abdominal cavity. The liver weighed 550 grams and appeared fatty. Numerous ecchymotic areas were present on the serosal surfaces of the gastrointestinal tract. Congestion of the esophagus and stomach was evident.

The right kidney weighed 350 grams, most of which represented hematoma. Part of this hematoma was subcapsular and compressed the kidney parenchyma. There was hemorrhage about the right ureter. The left kidney weighed only 30 grams. The bladder contained numerous cysts in the mucosa, some filled with clear fluid, others with extravasated blood. These cysts tended to obscure the urethral orifices.

The combined weight of the adrenals was 10 grams. Their clearly defined cortices measured approximately 1 mm. in thickness. The skull was not entered.

TABLE I.

DATE (YEAR—1957)	TREATMENT	HEMOGLOBIN (GM. PER CENT)	RED BLOOD CELL COUNT (10^6)	WHITE BLOOD CELL COUNT (10^3)	BASOPHILS	EOSINOPHILS	MYELOCYTES
May 3	amethopterin (2.5 mg. daily) blood, 300 ml.	5.2	1.6	9.05	0	2	0
May 10	blood, 190 ml. developed chicken pox	8.2	2.2	3.0	0	0	0
June 19		11.2		11.6	0	0	0
July 1	ACTH gel (40 U. twice daily)	8.2	2.8	2.7	0	0	0
July 12	6-mercaptopurine (37.5 mg. daily)	9.5	3.0	3.4	0	2	0
August 9		10.4		3.9	2	1	0
September 20		12.9		5.3	0	0	0
October 4	ACTH gel (50 U. twice daily) amethopterin (2.5 mg. daily)						
October 19	prednisone (25 mg. every 6 hours)	9.8		6.3	0	0	1
November 1		6.4	2.2	5.0	0	0	0
November 13	blood, 300 ml. × 2 whole body irradiation	12.3		7.8	0	0	0
November 14	5.8 billion marrow cells 275 c.c. packed red blood cells from marrow donor	9.5		0.450			
November 15	250 c.c. packed red blood cells from compatible donor	7.0		0.350	0	0	0
November 16	death	7.9		0.526 0.126	0	2	0

TABLE II. URINALYSIS AND SERUM CHEMISTRIES FOLLOWING IRRADIATION

Irradiation: November 13, 1957

	NOVEMBER 12, 1957	NOVEMBER 14, 1957	NOVEMBER 15, 1957	NOVEMBER 16, 1957	NOVEMBER 17, 1957
Urinalysis (24 output)		200 ml.	30 ml.	260 ml.	
Reaction	7.5	4.5	5.0	6.0	
Sugar	0	0	0	0	
Protein	0	3+	3+	3+	
Microscopic	Normal sediment	20 to 80 RBC per unspun high power field	Numerous RBC's	50 to 80 RBC per unspun high power field	
Serum					
Uric acid mg. per cent			34.8		44.6 terminal
Phosphorus mg. per cent			20.3		
Sodium mEq./L.			131.0		
Potassium mEq./L.			6.15		
Calcium mg. per cent			4.4		
CO_2 combining power mEq./L.			17.0		5.0
Chlorides mEq./L.			97.0		93.0
Nonprotein nitrogen mg. per cent			140.0		208.0
pH on serum			7.5		7.13

HEMOGRAMS

JUVENILES	BAND	POLYMORPHOCELLULAR	LYMPHOCYTES	MONOCYTES	BLAST CELLS	NUCLEATED RED BLOOD CELLS AND RETICULOCYTES (PER CENT)	PLATELETS (10^3)	BONE MARROW
2		2	68	2	22		3.3	Blast cell replacement
0	0	8	78	0	14	0	16.140	
4	8	36	10	4	38	1.9 Retic.	10.0	Still blast cell replacement
0	0	48	24	6	24		20.0	
2	4	28	60	4	0	8.0 Retic.	144.0	Blasts > 10 per cent erythroid hyperplasia
0	0	30	57	9	0		240.0	
0	2	46	40	11	1		120.0	Blasts < 30 per cent
4	2	26	51	2	14	15.0 Nuc. RBC 1.0 Retic.	31.0	
2	2	12	65	0	6	7.0 Nuc. RBC	8.5	Blast cell replacement
0	1	12	78	0	9	0.2 Retic.	27.0	
							17.0	
0	8	0	2	0	0		20.0	
8	29	0	11	0	0		29.0	

On microscopic examination the lungs showed some alveolar hemorrhage but no pneumonia or edema. The liver showed fatty metamorphosis. The spleen revealed no reduction in lymphoid tissue and no evident hematopoiesis. The adrenals were normal. The kidneys showed the intrapelvic and perirenal hemorrhage described earlier. Sections from the sternum and crest of the ileum showed blood-filled spaces lined by endothelium.

IRRADIATION

The radiologic treatment of this patient had two major phases: first, irradiation to destroy the acute leukemia cells and depress the antigen-antibody response to the point where the body would not react unfavorably to the bone marrow components administered as the second phase of therapy.

Except for the treatment of localized areas, irradiation of acute leukemia has long been abandoned since in this disease group all bone marrow components appear to be equally and highly radiosensitive. The effort as applied here, however, is directed toward a replacement by other bone marrow and therefore this should not be a factor. The level at which destruction of the leukemia cells would be accomplished was not known but it was assumed to be at, or short of, the lethal dose.

With regard to the antigen-antibody response, one can only rely on animal experimentation which indicates that the LD_{100} irradiation level is necessary to get a maximum take of the bone marrow transplant.[3, 4] This conclusion is indirectly supported by the failures with lower levels of irradiation in man.[5] It was decided to administer an estimated LD_{100} of irradiation. A lesser amount would risk failure both in the possibility of leaving leukemia cells intact and in not sufficiently destroying the immune response. Nonetheless, the level of irradiation still would be such that approximately one half of the patients would ordinarily die from it.

Since man does not readily submit to experimentation to determine lethal dose, these conclusions are not of the highest accuracy. Ten or so years ago the LD_{100} was considered to be in the range of 500 or 600 r delivered as an acute exposure (within a few hours); this estimate has now been raised to 700 to 750 r.[6]

Cobalt 60 gamma irradiation was used because of its excellent depth dose and the fact that it is constant the world over. Owing to limitations in the sizes of treatment cones, we took the cone off completely and therefore had a circular field. The treatment fields were overlapped according to careful calculations* so that a homogeneous dose resulted along the midline. The source to skin distance was 110 cm. Two fields were used anteriorly and two posteriorly. Optimal "mating" of the beams occurred when their central rays were 66 cm. apart, so that the fields were centered 33 cm. above and below the longitudinal midpoint of the patient. Since the patient was 103 cm. in length, the coverage was more than adequate. Circular fields cannot be as easily juxtaposed as can rectangular ones. In this instance, however, the extended source skin distance resulted in fields of large diameter. Consequently, the junction of the fields caused only a relatively minor reduction in irradiation to the child's flanks.

Five centimeters of lead were used to shield the orbits from the anterior fields and the testicles from both anterior and posterior fields. This lead reduced the direct radiation by approximately 93 per cent. Three hundred and ninety-five roentgens were delivered to each field in 25.7 minutes. The total elapsed time was approximately 3 hours, the additional time being necessary to set up the fields and placate the patient. Owing to the difference in thickness and to lack of homogeneity of the radiation fields, the tissue dose varied from a minimum of 608 r to a maximum of 790 r. It is considered that the over-all effect was that of approximately 700 r to the whole body.

HEMATOLOGIC ASPECTS

Dogs were used in establishing the method of marrow transplantation. Marrow was taken from both femora, mixed with the dog's plasma, and repeatedly passed through a stainless steel screen to make a smooth cellular suspension. A special 20 c.c. syringe was used for this procedure. One end of this syringe was fitted with a holder for stainless steel mesh which had squares of 0.307 mm^2 and 0.86 mm^2.[7] The larger mesh was used to break up the marrow stroma, the smaller mesh

*Calculations were made by Dr. Walter Mauderli, physicist, Department of Radiology, University of Arkansas Medical Center.

to break up cell clumps. After centrifuging, the fat was removed. In this manner 4.8 billion donor cells were obtained and given intravenously to a recipient dog without reaction. At autopsy there was no microscopic evidence of emboli in the lungs.

Theoretically, serotyping should not be significant in selecting a marrow donor for an irradiated patient. Nonetheless, we checked the mother and father and chose the latter because his serotype matched his son's and he had more available marrow. Under general anesthesia all accessible marrow from the posterior superior spine and posterior crest of the right ileum was removed with Cobb gouges. This marrow was cut into 1 cm. pieces and processed aseptically with the special syringe described above. One hundred and twenty-five cubic centimeters of the donor plasma containing 5.6 billion marrow cells were given to the child intravenously 3 hours after removal from the father.

At the time of death there was no evidence of marrow regeneration, although the last count of the peripheral blood revealed 8 band-type polymorphonuclear leukocytes but no promyelocytes or blast cells. The white blood cell counts were very low, the last one being 126 cells per cubic millimeter. The hemoglobin also dropped faster than expected, a fact probably explained by the bloody abdominal fluid and large right kidney hematoma

METABOLIC IMBALANCE

The increase of serum uric acid levels and increased uric acid excretion in acute leukemia is well documented.[9, 10] Normal serum uric acid values are 3.5 to 8.8 mg. per 100 ml. of serum, with urinary uric acid values being 5.2 to 7.3 mg. per kilogram per 24 hours.[10] Increases in serum uric acid and urinary uric acid levels have been found to be greater in the acute lymphocytic leukemias than in chronic lymphatic leukemia. Treatment with irradiation, steroids, 6-mercaptopurine, or amethopterin have all been found to increase the excretion of uric acid. In our patient the first serum uric acid value was obtained 48 hours after irradiation and was 34.8 mg. per cent. It had risen to 44.6 mg. per cent at the time of death.

Oliguria developed during the period of uric acid increase. Several factors may have contributed to the oliguria, proteinuria, and decreased renal function. Irradiation itself, since its effects on the kidneys are delayed, probably did not participate in the renal shutdown. Circulatory interference coincident with the enlarging kidney hematoma may have altered renal function. Impairment of renal function in the face of growing accumulations of tissue breakdown products may be enhanced by obstruction from uric acid crystals[11] and calculi, particularly in the presence of an acid urine. The presence of uric acid crystals in urine with a pH of 5.0 in an already oliguric patient was considered as an indication for ureteral and pelvic catheterization and flushing with sodium bicarbonate. This procedure may have augmented the hemorrhage about the right ureter seen at autopsy. The enlarged right renal shadow, however, had been noted 2 days previous to catheterization of the ureter and was coincident with a marked drop in hemoglobin. In the absence of almost all renal function the experience with this patient illustrates the rapidity

with which metabolic breakdown products will accumulate following irradiation, precipitating great shifts in electrolyte patterns. Despite the administration of sodium bicarbonate intravenously, acidosis became more pronounced, as reflected in the decreasing serum CO_2 combining power, pH, and chloride values associated with increasing nonprotein nitrogen levels.

Such magnitude of electrolytic imbalance following lethal irradiation has not been appreciated in animal experimentation but may be one of the serious problems involved. Although the same type of imbalance has been described by Gold and Fritz[13] relative to hydrocortisone therapy in acute leukemia, the irradiation effect may be less reversible. In both of their cases and in ours elevated serum potassium, phosphorus, creatinine, and uric acid values were found associated with low serum calcium, CO_2 combining power, sodium, and chloride values.

While the electrocardiographic evidence of hyperkalemia was present, there was tachycardia, cardiac irregularity, and extrasystoles in our patient. Electrocardiographic evidence of improvement occurred with the administration of glucose- and sodium-containing solutions. Clinically, tetany of the hands and feet was present at the time the electrocardiogram suggested hypocalcemic effect. The serum calcium was 4.4 mg. per cent and the phosphorus, 20.3 mg. per cent. The tetany responded temporarily to intravenously administered calcium gluconate.

DISCUSSION

Lethal irradiation followed by bone marrow transplantation is a form of therapy that is still relatively unevaluated in human beings.[14] McIlvanie[15] has pointed out two serious problems: (1) Acute leukemia is not necessarily eradicated by lethal whole body irradiation. (2) Septicemia may be the cause of death when the immune response is paralyzed by irradiation. Animal experiments further warn of other limitations to the use of bone marrow transplantation in human beings. There is a high incidence of delayed death in irradiated mice treated with rat bone marrow.[16] Van Bekkum and Vos[16] suggested this was due to an immune reaction, with the host or the donor tissue producing antibodies against the other. Makinodan[17] found no evidence of donor tissue antibodies against the host but did find the converse in irradiated mice treated with rat bone marrow. To circumvent this reaction, the use of fetal bone marrow has been suggested.[*] Undifferentiated fetal marrow may have a property of "acquired tolerance" when it is exposed to a fully developed antigenic system. Uphoff[18] describes two groups of mice who were equally well protected for a 90-day period by the use of isologous bone marrow or fetal hematopoietic tissue but were poorly protected by homologous marrow transplants. Since sepsis is difficult to prevent in human beings receiving lethal irradiation, Constandoulakis[19] has questioned how soon these fetal cells would be capable of immune reactivity such as would be necessary to resist infection in the host.

In the case presented here the problem of hyperuricemia with metabolic imbalance and renal failure had not been adequately anticipated as a complication of the lethal whole body irradiation and bone marrow transplant. In the treatment of acute leukemia

with antimetabolites and steroids this problem is minimized by alkalinizing the urine with sodium bicarbonate. This alkalinization should also be done prior to, and through, the period of cellular breakdown following radiation. Since the demands upon the renal system are great, any evidence of renal impairment might militate against whole body irradiation. By fractionating the dose of irradiation before transplanting bone marrow, it may be possible to "plateau" rather than peak the metabolic solutes necessarily cleared by the kidneys.

As a further adjunct in regulating the acid-base disturbances after irradiation, exchange transfusion might be considered. It has successfully reversed the effects of poisoning from boric acid,[20] isoniazid,[21] salicylates,[22] and in animals the products of uremia.[23] It might be advantageous to use blood from the marrow donor for the exchange transfusion, thereby automatically reserving this procedure for the small infant.

When the multiplicity of facets to the problem of lethal irradiation and marrow transplant are evaluated, a successful outcome to this procedure seems most improbable at the present time.

SUMMARY

The history of a patient with acute stem-cell leukemia in whom lethal irradiation and marrow transplant were tried after all conventional therapy had failed is presented. Hematologic and metabolic problems were encountered which were associated with renal failure and could not be overcome.

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"... my object has been to show that there exists in the child, and even in the infant at the breast, a nervous state, which precedes anatomical alterations in the nervous system, and which can often be attributed to heredity, alcoholism or to syphilis, but which may also originate in the mode of life of modern society and in disregard of the most elementary laws relating to the nutrition of the infant, whose normal development requires quietude and the absence of excitement of the brain, the senses and the general nervous system."

Jules Simon, M.D., from Cerebral Irritations in Young Children, and Especially Infants at the Breast, Transactions of the Ninth International Medical Congress, 1887.

THE TREATMENT OF ILEOCOLIC INTUSSUSCEPTION

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THE treatment of uncomplicated ileocolic intussusception in the United States has been predominantly surgical. This paper reviews the experience with 264 children with intussusception seen at the Children's Hospital of Pittsburgh from 1928 to 1956 and discusses treatment with hydrostatic pressure.

HISTORY AND LITERATURE

Hirschsprung[1] in 1876 first described the treatment of intussusception with hydrostatic pressure. In 1905, he reported a 35 per cent mortality rate in 107 children so treated. Lehmann[2] described the diagnostic roentgen features of intussusception in 1913. Clubbe[3] and Hipsley[4] reported on 834 and 100 patients with intussusception, respectively, treated by hydrostatic pressure. Retan[5] in 1927 reported the first successful treatment in the United States of ileocolic intussusception with hydrostatic pressure. In 1948, Ravitch and McCune[6] reported on 48 patients with intussusception in whom hydrostatic pressure was employed as the initial method of treatment. Fifteen of these 48 children required surgery to complete the reduction of intussusception. Hydrostatic treatment with barium enema has been the initial treatment of choice for children with uncomplicated ileocolic intussusception at the Children's Hospital of Pittsburgh since 1950.

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MATERIAL AND RESULTS

From 1928 through 1956, 264 children with ileocolic intussusception were examined at the Children's Hospital of Pittsburgh. The diagnoses were proved at surgery, by radiography, or at necropsy. One hundred and sixty-three children were treated by surgery alone. Between 1950 and 1956, 92 children were treated initially with hydrostatic pressure.

The ages of the children ranged from 1 month to 14 years, with the mode at 6 months. Two hundred and one children were younger than 2 years of age. The 28 Negro children with intussusception reflected the hospital admission ratio of white to Negro patients for all diseases. There were 185 boys and 79 girls. The incidence of intussusception showed seasonal variations, reaching peaks in the summer months of July and August.

Intussusception is a dynamic condition; the head of the intussusception is not in fixed position unless or until gangrene and adhesions occur. Stretch on the mesentery produces periodic shocklike episodes and circulatory embarrassment, the latter resulting in passage of blood in the stool.

Gangrene may be an early or late occurrence, depending on the extent of vascular embarrassment.

Ileocolic intussusception is an idiopathic condition usually occurring in previously healthy children. There is no regular antecedent history; the condition is heralded by attacks of severe paroxysmal abdominal pain associated with pallor. Vomiting, palpable abdominal mass, and blood in the stools are often present. Any or all of the clinical findings may be absent in the individual case.

Table I. Presenting Symptoms and Signs

		(per cent)
Vomiting	217	82
Blood in stool		
By history	172	65
On examining finger	126	48
Pain	219	83
Palpable abdominal mass	180	72
	(Total 264 cases)	

Peritonitis, shock, severe dehydration, and high fever implied poor prognoses (Table III). Often these findings

Table II. Duration of Symptoms Related to Mortality

Days before treatment	Number of patients	Number of deaths
1	145	13
2	50	11
3	19	3
4	16	3
5	9	2
6	2	0
7	6	2
Over 7 days	13	0
Totals	260*	34*

*Not included in this table are the 3 agonal instances of intussusception and 1 death that occurred in a child with history of recurrent intussusceptions for more than 3 years.

Table I summarizes the incidence of these findings.

Thirty-eight deaths occurred among the 264 children with intussusceptions. Six children died before they had received any form of definitive treatment. In 3 other children intussusceptions were agonal and identified as incidental findings at necropsy.

Twenty-seven deaths occurred among the 163 children treated by surgery alone. One death occurred in the group of 92 children treated only by hydrostatic pressure. There was one death in an infant treated by initial hydrostatic pressure and subsequent surgery.

Table II shows the mortality rate related to duration of symptoms prior to institution of therapy. There were 2 deaths in the group of 21 children whose symptoms had lasted 6 days or longer.

occurred together in the same patient. White blood cell counts were done on 173 children. These bore no obvious relationship to the prognosis.

Recurrences of intussusception were recorded in 12 children, 6 of whom had been treated initially by surgery and 6 by hydrostatic pressure. These occurred as early as 12 hours and as late as 3 years after initial reduction of the intussusception, but were most common during the first 24 hours.

Lead points were present in 23, or 8.7 per cent of the 264 instances of intussusception (Table IV).

TABLE III. FINDINGS ASSOCIATED WITH POOR PROGNOSIS

	CASES	DEATHS
History of cathartics	25	6
Fever (102° F.)	25	13
Abdominal distention (marked)	55	16
Rectal mass	25	8
Shock	60	21
Dehydration (severe)	35	15
Peritonitis	30	15
(Age less than 4 months	14	7)

METHOD

The methods employed in the hydrostatic reduction of uncomplicated ileocolic intussusception at the Children's Hospital of Pittsburgh have been described by Girdany and co-workers.[7, 8] Signs of intestinal obstruction suggest the presence of ileo-ileal intussusception or gangrene and are contraindications to the use of hydrostatic pressure.[8] The radiologist applies hydrostatic pressure with barium enema, with the surgeon in consultation and attendance. The child with intussusception must be in satisfactory clinical condition to tolerate the hydrostatic procedure. Shock and dehydration are corrected before any definitive treatment of intussusception is undertaken.

The radiologist introduces a thin mixture of colloidal barium and physiologic saline solution into the rectum and follows the progress of the mixture fluoroscopically. The intussusceptum causes a typical filling defect in the barium column which recedes in front of the onflowing barium mixture. The radiologist exposes spot films for later study as indicated. He considers reduction of ileocolic intussusception complete when he observes the free flow of the barium mixture through the ileocecal valve and into the ileum. The hydrostatic procedure is terminated if the barium mixture does not enter the ileum from the cecum after 5 minutes.

TABLE IV. INCIDENCE OF LEAD POINTS

Total number of cases of intussusception was 264	
Meckels diverticulum	8
Polyp	6
Duplication	4
Aberrant pancreas	1
Stenosis of ileum	1
Enlarged lymph nodes	3
Total	23

Ileal filling is the single most important roentgen criterion of completeness of reduction of intussusception. Without this sign the radiologist cannot declare reduction complete. In some normal children reflux of opaque material into the terminal ileum is not achieved during routine barium enema studies. A large filling defect at the ileocecal valve, suggesting incompleteness of reduction, may be due to residual edema of the mucosa.

RESULTS OF TREATMENT WITH HYDROSTATIC PRESSURE

From 1950 through 1956, 92 children with intussusception were treated initially by hydrostatic pressure. In 80 hydrostatic pressure was definitive therapy. In 3 of these 80 children the roentgen signs of reduction of intussusception were not certain and surgical exploration was carried out. At surgery, reduction was found to have been completed.

Eleven children had intussusceptions not reduced by hydrostatic pressure. Seven of these were ileo-ileocolic in nature. Three of the failures of reduction which occurred during the early experience with the hydrostatic method were not explained at surgery. These intussusceptions were reduced without difficulty at laparotomy.

Perforation of the colon occurred in one 3-month-old infant with ileocolic intussusception associated with gangrene. This infant made an uneventful recovery after surgical resection of the gangrenous bowel.

One 3-month-old infant, who had received castor oil and who was presented in shock, was considered too ill for surgical treatment. At the request of the attending surgeon, hydrostatic pressure was applied. The intussusception was reduced, but the infant died 2 days later. At necropsy the intussusception had not recurred, and the infant's bowel was not gangrenous.

A 6-month-old infant with ileo-ileocolic intussusception had an unsuccessful reduction of intussusception by hydrostatic pressure which was followed by resection of gangrenous bowel at surgery. He died 6 hours after surgical treatment. The hydrostatic procedure was carried out while the operating room was being prepared and did not delay surgical treatment.

Filling defects in the terminal ileum during successful hydrostatic reductions of intussusception indicated lead points in 2 children. At subsequent surgery a polyp and an ileal duplication, respectively, were resected.

Six children initially treated with hydrostatic pressure had recurrences of their intussusceptions. Two were treated again with hydrostatic pressure and made uneventful recoveries. The other 4 children were operated upon. In one of them an hypertrophied lymph node was thought to be the lead point of intussusception. Lead points were not demonstrated in the remaining 3 instances.

Twenty-five children with symptoms persisting longer than 48 hours had successful reductions of their intussusceptions with hydrostatic pressure. This confirms the impression that duration of symptoms is not a necessary contraindication to treatment with hydrostatic pressure and demonstrates the dynamic nature of intussusception.

The average hospital stay after surgical treatment of intussusception was 12.4 days; for hydrostatic pressure it was 3.1 days. Fever was rare in children following successful hydrostatic treatment of intussusception. It was common following surgical reduction.

DISCUSSION

The objections that have been raised to the use of hydrostatic treatment of intussusception include the suggested possibilities of perforation or reduction of gangrenous bowel, of failure to

identify lead points, of increased incidence of recurrences, and of uncertain identification of completeness of reduction.

Ravitch and McCune[6] experimentally showed in dogs that 3 feet of hydrostatic pressure would neither reduce intussusception in, nor rupture, gangrenous bowel. In the series presented here perforation of normal colon distal to the site of gangrene in ileocolic intussusception occurred in one infant after the enema tubing was "milked" to promote the flow of solution. Complete intestinal obstruction produces a closed hydrodynamic system. Compression of the tubing produces major increases in intralumenal pressure similar to that effected by the pressure of a foot on the brake pedal in an hydraulic system. This amount of pressure far exceeds that of 3 feet of water. Three of the children with ileo-ileal intussusceptions had gangrenous bowel resected at surgery. In these instances hydrostatic pressure neither reduced the intussusceptions nor perforated gangrenous bowel. Available evidence supports Ravitch's observations.

Lead points were demonstrated radiographically in 2 children whose intussusceptions were reduced by hydrostatic pressure. In one instance of recurrence after reduction by hydrostatic pressure, a swollen patch of lymphoid tissue was the lead point of the recurrent intussusception. In the other patients operated upon following recurrences of intussusception, no lead points were identified. Included among the children who had recurrent intussusception following initial surgical reduction, there was one with an ileal duplication that had not been recognized at the time of the initial surgical treatment. In a child referred to us, and not included in this series, a filling defect was identified on barium enema studies in the distal ileum. This child had had two previous surgical reductions of intussusception. After the intussusception had recurred for the fourth time, surgical reduction of the intussusception and removal of an ileal duplication were done.

In the series reported here, as in observations elsewhere, there was no increase in recurrences following hydrostatic reduction of intussusception as compared to those reduced primarily by surgery.

Failure of recognition of incompleteness of reduction cannot occur if the roentgen criteria are rigidly followed.

Morbidity studies show some of the advantages of the nonsurgical method of reduction of uncomplicated ileocolic intussusception. Other advantages include comfort to the patient, shortened hospital stays, and avoidance of major laparotomy.

No valid differences in mortality exist in the experiences discussed here and in the literature between hydrostatic and surgical reductions of intussusceptions. Deaths are more often the result of gangrene, shock, dehydration, and the over-all condition of the child than the method of definitive reduction of his intussusception. No method of treatment should be applied until the patient is in condition for its application. In the results recorded here 6 children died before any form of definitive therapy could be initiated. The infant who died 2 days following reduction of intussusception by hydrostatic pressure was

moribund at the time of admission and convulsed during the hydrostatic procedure. The infant who died following the attempt at reduction by hydrostatic pressure and the subsequent surgical reduction of the intussusception and resection of gangrenous bowel succumbed 6 hours after surgery. In each of these cases definitive treatment was an emergency procedure in a moribund infant. It is not proper to argue the merits of hydrostatic against primarily surgical methods of treatment in these instances, as it would not have been in those 6 infants who died before any definitive treatment could be instituted.

CONCLUSIONS AND SUMMARY

1. The experience with 264 patients with intussusception is reviewed; 92 children with ileocolic intussusception were treated initially with hydrostatic pressure.

2. Morbidity and length of hospital stay were favorably affected by hydrostatic treatment.

3. Prolonged duration of symptoms is not a necessary contraindication to treatment by hydrostatic pressure. No definitive treatment should be attempted until shock and dehydration have been corrected.

4. The incidence of presenting signs and symptoms in a group of 264 children with intussusception is reviewed.

5. Mortality with intussusception is related to gangrene, prolonged intestinal obstruction, electrolytic disturbances, shock, and the presenting condition of the patient. There is no valid difference in mortality rates between the primarily surgical and the hydrostatic methods of treatment.

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SURGICAL REMOVAL OF A RUPTURED INTERVERTEBRAL DISC IN EARLY CHILDHOOD

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THE typical signs or symptoms of a ruptured intervertebral disc in the lumbar region in a 3-year-old child are infrequently encountered. It is even more unusual to verify them by operative removal. No report of a similar case at this age, in which an operation was performed, has been located.

CASE REPORT

A 3-year-9-month-old boy (N. P.) was admitted to the pediatric section of the Robert Packer Hospital on March 11, 1958, because of inability to walk. He had been perfectly well until 19 days before admission, at which time he cried out because of sudden onset of severe low back pain. It occurred as he was arising from a toilet seat. For the next 4 days he walked about with great effort, holding his back rigidly. After this and until he was seen here, he refused to walk at all. The child would lie quietly in bed on his back with his knees flexed. He would not voluntarily stand, sit, or roll over. Whenever any attempt was made to change his position, he would cry and complain bitterly of pain in the low back and in both legs.

During the course of this illness, the child had a temperature of 103° F. for two or three days. This subsided spontaneously and the reason for the elevation is not known. A review of the history disclosed that the child had had a few of the childhood illnesses, none of them seriously.

On admission the temperature was 99° F. (rectally), pulse, 90, and respirations, 24. The child was well developed, well nourished, and looked the picture of health. So long as he was left quietly alone, he appeared comfortable. When asked where "it hurt," he pointed to the right lumbar, paravertebral, and sacroiliac regions.

The neck was held rigidly and when passively flexed, the child cried out, complaining of low back pain. No other abnormalities of the head, neck, or cranial nerves were detected. Examination of the arms, chest, and abdomen likewise revealed nothing abnormal. The lumbar paravertebral muscles were rigid, and there was marked tenderness to even mild pressure over the L3, L4, and L5 spinous processes. The child could not be induced to sit or stand. When lifted up by his arms, his crying was loud and voluble. He kept his legs tightly flexed on his abdomen and he refused to straighten them out or to remain in a kneeling or sitting position. When put back in bed, he would scream until he was placed flat on his back, following which all protests quickly subsided. The legs themselves were not remarkable; all reflexes were normally active except for the right patellar, which was markedly diminished.

Laboratory Studies.—The red blood cell count was 3,000,000 per cubic millimeter; hemoglobin, 10 Gm. per cent; white blood cell count 9,300 per cubic millimeter, with a normal differential. Serologic test for syphilis was negative. Roentgenograms of the thoracic and lumbar spines and the pelvis were normal. An intravenous pyelogram was likewise normal. Tuberculin tests were consistently negative (Fig. 1).

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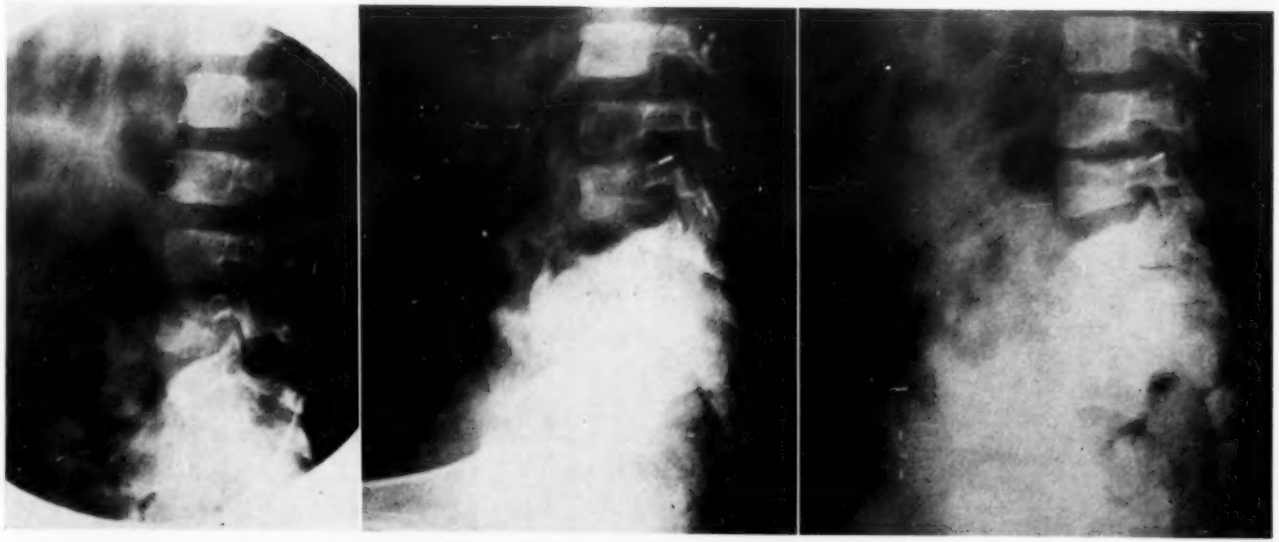

A. *B.* *C.*

Fig. 1.—*A*, Roentgenogram taken on admission. No specific lesion noted. *B*, Roentgenogram taken 10 days after operation. Interspace from which disc was removed has been marked by a silver clip. *C*, Roentgenogram taken 6 months after operation. No essential change noted when compared with original films. No evidence of osteomyelitis or eosinophilic granuloma.

When I first saw the child, a few days after admission, his condition was essentially unchanged. He still refused to stand or sit and would scream violently if placed in these positions. The right knee reflex was almost absent. The straight leg raising test was positive when lifting either leg just a few degrees off the bed. Although the child was alert and intelligent, I was unable to explain what numbness and paresthesias were so that even if the child experienced them, he was unable to tell me about them. No definite areas of hypesthesia could be demonstrated by the use of a pin.

The urine was tested on several occasions for this substance, without a positive reaction (Fig. 2).

Since our collective experience with protruded discs at this age was severely limited, it was decided to be conservative for another week. During this period the child did not improve. There were some irregular temperature elevations up to 100° F. (rectally).

On March 20, 1958, a lumbar exploration was done. A very large protuding disc was found at the L4-L5 interspace, which required a hemilaminectomy for adequate exposure and removal. The disc material

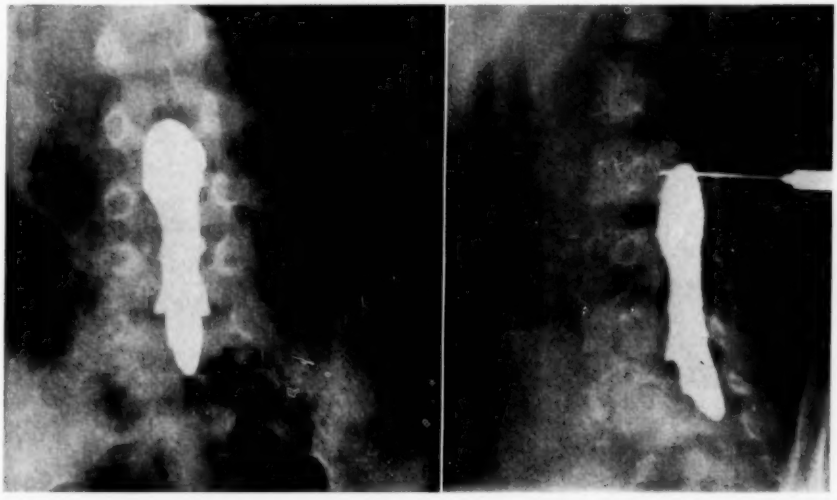

Fig. 2.—Myelogram showing a large defect in the column of oil, on the right, at the L4-L5 interspace.

When pressed for an opinion regarding the child's illness, the possibility of a spinal cord tumor seemed most likely. The possibility of a ruptured intervertebral disc was timorously suggested and it was received with the skepticism expected.

A myelogram was obtained and a large defect at the L4-L5 interspace was clearly demonstrated. It looked like an extradural mass, either a neoplasm or extruded disc. The latter immediately suggested alkaptonuria. looked exactly like that found in extruded discs in adults. All the disc material that could be curetted out of the interspace was removed. Unfortunately, a culture was not taken simply because it never crossed the operator's mind. There was nothing to suggest an infectious process.

The postoperative course was complicated by a sharp initial rise in temperature to 103° F. (rectally), with a slow, irregular fall to normal by the eleventh postoperative day. There was

no sign of a wound infection. The possibility of osteomyelitis was entertained but not substantiated. It was finally concluded that the child had a respiratory infection due to the operative procedure which required general anesthesia administered for about one hour with the child in a prone position.

During follow-up visits the mother reported the child acted in a normal manner. He ate, slept, got up, ran, played, and tumbled about without restriction or complaint. The legs were strong. The knee reflexes were brisk and equal. The ankle reflexes remained normal. To the examiner, the child seemed normal. He had

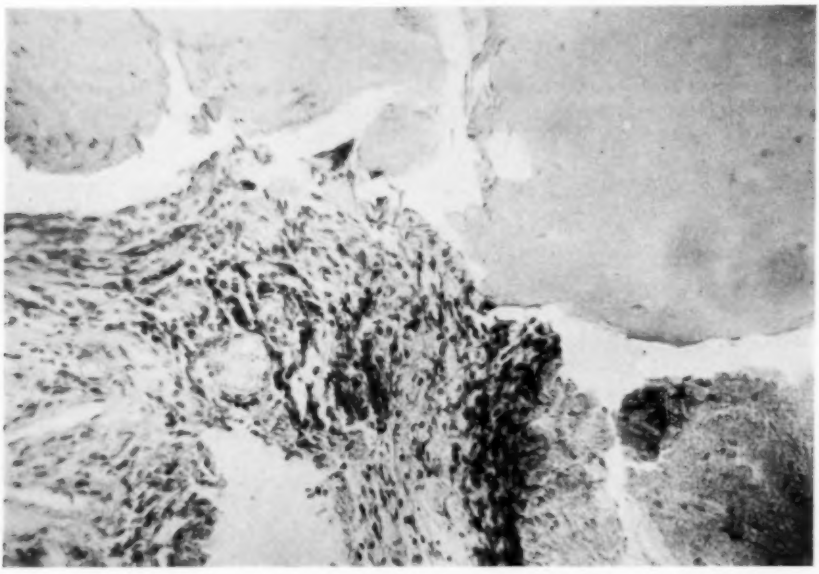

Fig. 3.—Microscopic section of material removed at operation. Area of granulation tissue infiltrated by cells indicating chronic infection is seen between areas of cartilage and nucleus pulposus. Giant cells of the Langhans type were not seen (reduction ¼).

The external wound healed quickly and well. The child did not protest being rolled over in bed after the third postoperative day, and within a week he sat and stood up spontaneously. He had not been urged to roll, sit, or stand since it was desired to see when he would do so without prodding or encouragement. By the time of discharge on the fifteenth postoperative day, the child voiced no complaints. He was running about the ward, sitting in a chair, and playing with the other children. The stiffness of the back had subsided to a large degree and he was spontaneously bending it to pick up objects off the floor.

made a recovery that was far more satisfactory than is usually made by adults after an intervertebral disc is removed. Postoperative roentgenograms taken 4 months after the operation appeared normal. There had been no significant narrowing of the L4-L5 interspace. The bones showed no signs of sclerosis or infection.

Pathologic study of the excised disc material showed areas of granulation tissue interspersed between normal areas of disc material. Other areas were infiltrated by polymorphonuclear neutrophils, lymphocytes, and monocytes. The pathologist suggested an

acute infection of the disc and surrounding bone. The postoperative course and the roentgenograms indicate a complete healing of the process (Fig. 3).

It has been suggested that the pathologic findings might be those surrounding an eosinophilic granuloma. Roentgenograms of the surrounding bone had not indicated such a process and further sections of the material removed at operation failed to substantiate such a diagnosis. Such a possibility, however, cannot be entirely dismissed.

COMMENT

In recent years there have been several publications concerning disc disease in children. Most authors stress either infection or disturbances of metabolism as etiologic possibilities; trauma is rarely suggested as a possible cause, in contradistinction to reports on disc disorders in adults.

In the very young discs in the thoracic region appear to be more prone to disorder than those in the lumbar region, again in marked contrast to the situation in adults. Silverman,[1] Peacher and Stoors,[2] and Walker[3] have discussed instances of calcification of intervertebral discs in childhood. Crosett[4] reported the occurrence of this condition in a child 2½ years of age; this is one of the youngest cases recorded. No definite etiology has been established to account for the calcification. Infection, faulty metabolism, and trauma have been suggested as possible causes but have not been verified. Over a period of weeks the acute symptoms subside and the calcification seems to diminish as the child grows.

Calcification of the intervertebral disc is usually a benign process. However, Walker's[3] patient prolapsed disc material into the spinal canal. Peck[5] reported on a 12-year-old boy who also prolapsed such a disc at the T-6 level and who required surgical intervention. The material removed at surgery was described as an amorphous calcified mass. This was quite different from the case under discussion here since the material recovered at operation appeared to be the same sort of disc material found at operations of adult patients.

It cannot be stated categorically that our patient might not have developed calcification in the affected interspace had the disc material not been removed at operation. It seems unlikely, however, because if one may gauge the interval between the onset of symptoms and the appearance of calcium in the roentgenogram, there had been sufficient time to develop it. Certainly calcium deposits should have been visible in the material removed at operation.

Mathews and associates[6] have described back pain in children 2 to 3 years of age. It is often associated with signs of infection which the authors assumed involved the intervertebral discs. None of the children had root signs and the disorder subsided spontaneously. Their description did not seem to fit the case under discussion.

In the absence of alkaptonuria, any evident preceding infection, and a normal roentgenogram of the spine, I do not believe that the protruding disc was due to any of the above-mentioned disorders. The history, location of the protrusion, and the operative findings all simulate those of adults. Since we have little definite information as to the fundamental disorder that allows discs in adults to

prolapse, it is conceivable that the same process occurred in our child, with exactly the same results. Trauma, to me, has always seemed incidental to the condition of disc "rupture" or prolapse, except in those cases where trauma to the back has been so devastating that disc extrusion has only been a part of the injury along with fractures and dislocation of the vertebra, trauma to the cord, avulsion of ligaments, and tears in the muscle.

The proper method of treatment engendered much discussion by the physicians who saw the child. Conservatism was the consensus of opinion initially, but after a month of continued symptoms and the possibility of serious injury to the L4 root, there appeared to be no valid reason why surgery should not be used.

There is little in the literature to use as guidance. Webb, Svien, and Kennedy[7] reviewed a large series of disc operations and found only 5 patients with an age of less than 16 years. Their youngest patient was 12 years of age. All protrusions were at the L4-L5 level. Key,[8] in his discussion of the subject, emphasized that the signs and symptoms in children were often different from those in adults and that the typical pattern was rare. Nearly all got well with conservative care, but about 10 per cent required operation for relief of pain. His youngest patient was 14 years of age. In view of the rather typical history, signs, and symptoms, together with failure of conservative care after one month, and the excellent result following surgery, it would seem that there is no serious contraindication to operative removal of a prolapsed disc in children, irrespective of the age, if other methods of treatment fail.

SUMMARY

An instance of a protruded disc in a child 3 years of age is reported. Recovery following surgical removal was complete, after conservative measures had failed. The literature on disc disorders in children is briefly reviewed.

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BUDD-CHIARI SYNDROME

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IN 1846, Budd[1] in his textbook "Diseases of the Liver," briefly described a symptom-complex produced by thrombosis of the hepatic veins. Lambron first reported this condition in 1842. In 1899, Chiari[2] reported three autopsied cases with similar clinical manifestations following thrombosis of the hepatic veins. Since then, the condition has commonly been known as the "Budd-Chiari syndrome." Palmer[3] has listed the etiologic factors. Following the comprehensive review of the literature by Palmer, other reports have appeared,[4-7] with antemortem diagnoses confirmed by catheterization of the hepatic veins and venography. The youngest age of an affected child recorded was 17 months. This paper reports a case in a child 18 months of age.

CASE REPORT

An 18-month-old white girl was hospitalized on June 12, 1958, because of abdominal distension and ascites. The family history was significant in that the child was one of identical twins, the sibling was in excellent health.

Past History.—The patient had frequent bouts of upper respiratory infections, vomiting, diarrhea, and mild anemia during the 6 months prior to admission. The anemia was considered to be secondary to a poor dietary intake, and iron medications had been prescribed; these were thought to be a factor in the frequent bouts of vomiting and diarrhea. Three days prior to admission the parents noted abdominal distension, anorexia, and irritability. There had been no vomiting and stools had been normal. Attempts by parents to relieve the distension with enemas were unsuccessful. She was taken to a US Air Force Dispensary on June 12 and transferred to a US Army Hospital because of possible intestinal obstruction.

Physical Examination.—The temperature was 100.5° F. and the weight, 22 pounds. She was considered to be well nourished and well developed. There was pallor, abdominal distension, generalized abdominal tenderness, and ascites. The liver was about 10 cm. below the right costal margin. The spleen was not palpable. Bowel sounds were normal. The remainder of the physical examination was essentially negative.

Laboratory Studies.—The white blood cell count was 11,000 per cubic millimeter, with a normal differential. The red blood cell count was 3.2 million, and the hemoglobin, 8.2 Gm. per cent, with a hematocrit of 35 per cent. The urine was normal. The blood sugar and urea nitrogen levels were within the normal range. The serum bilirubin was 1.9 mg. per cent (direct, 0.19; indirect, 1.72); thymol turbidity was 6.0 U., and the cephalin flocculation, 3+. The serum protein was 6.3 Gm., with an A/G ratio of 1. Roentgenograms of the chest and long

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bones and the excretory urogram were normal. Examination of the bone marrow did not reveal any abnormalities.

Course.—Two days after admission a laparotomy was performed; the liver was noted to be enlarged and had a nodular surface. There was moderate ascites. No masses or lymph nodes were palpable and the kidneys were normal. A wedge biopsy of the liver was obtained, and ascitic fluid was collected for cytologic studies.

The initial study of the liver biopsy resulted in an erroneous diagnosis of neuroblastoma, and radiation therapy was instituted to the liver area on the second postoperative day. Review of the liver biopsy at another laboratory revealed no evidence of malignancy, the only finding was marked congestion and hemorrhage in the liver parenchyma. At the time, this was considered to be related to the biopsy procedure. Cytologic studies on the ascitic fluid revealed no abnormal cells. Radiation therapy was discontinued after 2 days. On the fifth postoperative day she developed more ascites and respiratory distress. A repeat chest film revealed no pulmonary involvement other than high diaphragms. A paracentesis was performed, and 900 c.c. of straw-colored fluid was removed. She was afebrile, except for a low-grade temperature of 100 to 101° F. for 2 days postoperative. On the eighth postoperative day she developed clinical icterus. The liver decreased in size and her condition deteriorated. She was considered to have a severe toxic hepatitis and administration of corticosteroids, parenteral fluids, and vitamins was begun; penicillin and streptomycin, which had been started postoperatively, were continued. The ascitic fluid reaccumulated rapidly, necessitating repeated paracenteses. An extensive thrombophlebitis developed at the site of the venous cut-down at the right ankle. The serum bilirubin rose to 5.5 mg. per cent (direct, 2.0; indirect, 3.5), and the prothrombin time was 58 per cent of normal. The total serum protein was 4.4 Gm. per cent, with an A/G ratio of 1. Other blood chemical studies revealed a normal carbon dioxide combining power and normal serum sodium, chloride, potassium, and cholesterol levels. The urine contained bile. The course was downhill and she was transferred to another US Army Hospital on the sixteenth postoperative day. Oral feedings were taken poorly, and she required frequent abdominal paracenteses to relieve the severe abdominal distension. Small blood transfusions were given because of low hemoglobin levels, and she also received antibiotics and parenteral fluids. She developed hematemesis and melena, became unresponsive, and expired on the twenty-second postoperative day. An autopsy was obtained.

Postmortem Findings.—A complete autopsy was performed 11 hours after death. The principal findings were in the liver. Grossly, the liver was bluish-red and hard, with approximately a 40 per cent increase in weight. Five hepatic veins emptied separately into the inferior vena cava. These were greatly reduced in size and completely occluded. Sectioning of the organ revealed extension of the thrombotic process into the parenchyma.

Microscopic examination revealed the hepatic and central veins to be dilated, with the walls greatly thickened by dense fibrous tissue. Minimal inflammatory cells were present in the vicinity of these vessels. There were thromboses in various stages of organization. The hepatic parenchyma was markedly congested with pronounced central lobular degeneration. Fig. 1 reveals an organizing thrombus with congestion of surrounding liver parenchyma. Other fields reveal fibrosis of the parenchyma, severe congestion, and organized fibrotic thrombi. The vessel wall is thickened and noninflammatory.

Additional pathologic findings included evidences of septicemia (pseudomonas and *Staphylococcus aureus,*

coagulase positive), with multiple abscesses and an interstitial pneumonitis of all lobes of the lungs. There were multiple, acute ulcerations of the stomach and duodenum, and the stomach and small intestines were markedly distended. Thromboemboli were present in the spleen, pancreas, adrenals, kidneys, and ovaries, and there was thrombophlebitis of the right femoral vein. Vascular shunts were found in the peritoneum adjacent to the liver and in the right pericolic gutter. There was generalized abdominal lymphadenopathy.

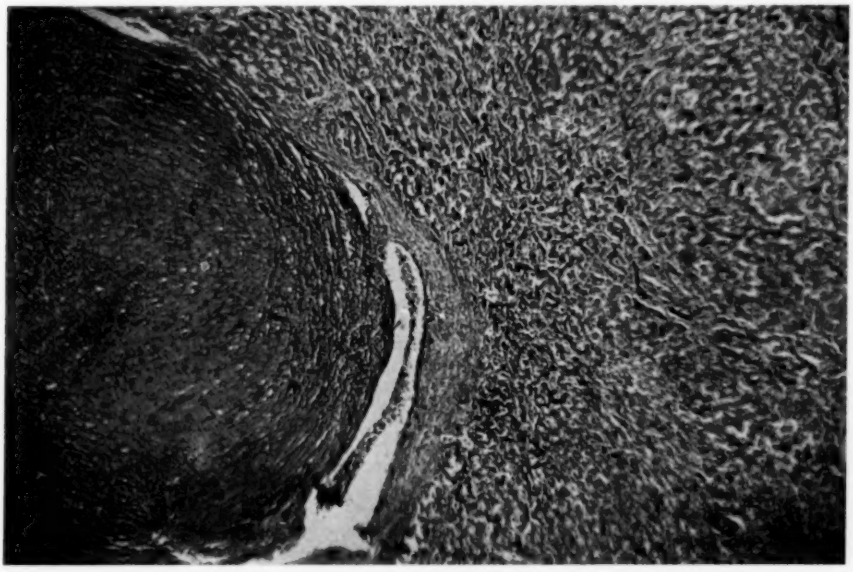

Fig. 1.—Photomicrograph of liver of patient with Budd-Chiari syndrome which shows organizing thrombus with congestion of surrounding liver parenchyma (reduction ¼).

DISCUSSION

From the beginning, this patient presented a diagnostic problem. Originally neuroblastoma was considered as the most probable diagnostic possibility. Other possibilities considered were retroperitoneal sarcoma, hepatoma, Wilms's tumor, lymphoma, Letterer-Siewe's disease, von Gierke's glycogen storage disease, and galactosemia.

Since the gross appearance of the liver at the time of laparotomy together with examination of the excised tissues were initially thought to be consistent with the diagnosis of neuroblastoma, radiation therapy was instituted. Subsequent review of the biopsy material, however, was interpreted as showing no pathologic abnormality, and radiation therapy was discontinued. The patient pursued a progressive downhill course despite symptomatic and supportive measures.

A diagnosis of the Budd-Chiari syndrome was suggested by Lt. Col. Eddy D. Palmer, MC,* who saw the patient in consultation shortly after transfer to the U.S. Army Hospital at

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Landstuhl. His diagnosis was based on the sudden onset of hepatomegaly and ascites in a child in a good state of nutrition and with no previous clinical evidence of hepatic or cardiovascular renal disease. A portal venogram and measurement of the blood pressures in the portal system at the time of laparotomy might have resulted in a definite diagnosis of hepatic vein obstruction. The patient's precarious state at the time of transfer on the sixteenth postoperative day precluded a second laparotomy and diagnostic studies.

In the event that the correct diagnosis had been made at the time of laparotomy successful treatment would have been unlikely. The cases reported by Brink[4] and Hackensellner,[5] with diagnoses made by venography antemortem, both succumbed despite attempts to improve venous drainage with a portacaval shunt and splenectomy.

The pathogenesis of this patient's disease was apparently a chronic obliterative process in the hepatic and central veins with eventual acute massive thrombosis of these vessels. The result was hepatic insufficiency. The chronicity of the process is suggested by the peritoneal vascular shunts and the fibrotic changes in the veins. The pulmonary infection was superimposed on the patient's debilitated state. Terminally, the patient developed a septicemia. The duration of the primary disease is, of course, not known.

SUMMARY

The case of an 18-month-old girl with the symptom complex of abdominal distension, ascites, and hepatomegaly is presented. The original diagnosis was metastatic neuroblastoma. This diagnosis was erroneously supported by an initial pathologic report, and the patient was subjected to 2 days of radiation therapy before a review of the biopsy material was adjudicated as showing no liver pathology. The patient pursued a progressively downhill course, with recurrent ascites, jaundice, extensive thrombophlebitis, and death. At autopsy she was found to have thrombosis of the hepatic veins, consistent with the Budd-Chiari syndrome.

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FACIAL PARALYSIS ASSOCIATED WITH OSTEOPETROSIS (MARBLE BONES)

Report of a Case of the Syndrome Occurring in Five Generations of the Same Family

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FACIAL paralysis in association with osteopetrosis is a syndrome which as far as can be determined from a careful review of the medical literature has not been reported. For this reason, the occurrence of this syndrome in a child and in 13 other members in 5 generations of the same family is reported.

CASE REPORT

L. C., an 11-year-old boy, was apparently well until the morning of August 2, 1956, when his mother observed that he had difficulty in chewing his food and that the right side of his face was paralyzed. On the preceding day he had complained casually of an earache on the right side. Two days prior to the onset of the facial paralysis a dentist had inserted a filling in a right lower molar tooth. The tooth was said to be free of infection. There was no history of recent respiratory infection. He had had the usual childhood diseases from which he had made uneventful recoveries. He had always participated actively in athletics.

Physical examination, which was made 24 hours following the onset of the facial paralysis, revealed a well-developed and well-nourished 11-year-old boy, whose weight was 90 pounds and whose height was 57 inches. The ear canals and both drum membranes appeared normal. His hearing was normal in both ears. Opthalmoscopic examination revealed normal fundi. His vision was 20/20 bilaterally and the visual fields were within normal limits. There was weakness of the orbicularis oculi muscle on the right side, and he was unable to close the right eye completely. There was a masklike expression of the right side of the face (Fig. 1). The corner of the mouth was deviated to the left during smiling, giving the characteristic appearance which is indicative of a seventh cranial nerve paralysis on the right side. The remaining cranial nerves were intact. The reflexes were normal throughout. There was congenital absence of 2 bicuspid teeth. The physical findings were otherwise within normal limits.

The hemoglobin was 15.1 Gm., and the hematocrit was 43 per cent. The white blood cell count was 7,200, with 42 per cent neutrophils; 2 per cent eosinophils; and 56 per cent lymphocytes. The blood calcium was 4.9 mEq. per liter; total protein, 6.4 Gm.; albumin, 4.6 Gm.; globulin, 1.8 Gm.; A/G ratio, 2.5:1; alkaline phosphatase was 8.4 and acid phosphatase was 0.9 (Bodansky units).

Roentgenograms of the long bones (Fig. 2), the pelvis (Fig. 3), the spine (Fig. 4), and the skull (Fig. 5) showed marked increased thickness of the cortex characteristic of osteopetrosis. The skull showed increased density, especially in the petrous portion of the temporal bone. Similar bone changes were found in roentgenograms taken of the patient's father

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and 8-year-old brother. Special detailed roentgenograms of the mastoid region revealed encroachment by thickened bone on the seventh nerve as it passed through the stylomastoid foramen on the right side (Figs. 6 and 7). Roentgenograms of the left mastoid region revealed that there

Fig. 1.—L. C., 11 years of age, with paralysis involving the right side of the face.

was no bone encroachment in the region of the left stylomastoid foramen.

The family history revealed that the patient's father had osteopetrosis with bilateral facial paralysis which had been present since he was 12 years of age. An 8-year-old brother also had marble bones, but at the time of our study he showed no evidence of facial paralysis. The patient's paternal grandfather died in 1943 at the age of 56 in the Illinois Research Hospital. His hospital record revealed that he had residual facial paralysis on the left side and osteopetrosis; the cause of death was "leptomeningeal sarcoma with involvement of the left orbital sphenoid ridge." In a further study of the family history it was found that 13 patients afflicted with osteopetrosis with facial paralysis had occurred in 5 generations. All of the individuals in this study were males (Fig. 8).

Fig. 2.—Left humerus shows increased density of bone with increased thickness of the cortex. Father and brother show similar bone changes.

Since the pathology of osteopetrosis has been reviewed in the literature by Pierie,[3] Clifton,[4] and others,[5-7] it will be discussed in this report only as it is related to the cause of seventh nerve paralysis. Osteopetrosis is characterized by faulty resorption of the cartilaginous ground substance during endochondral bone

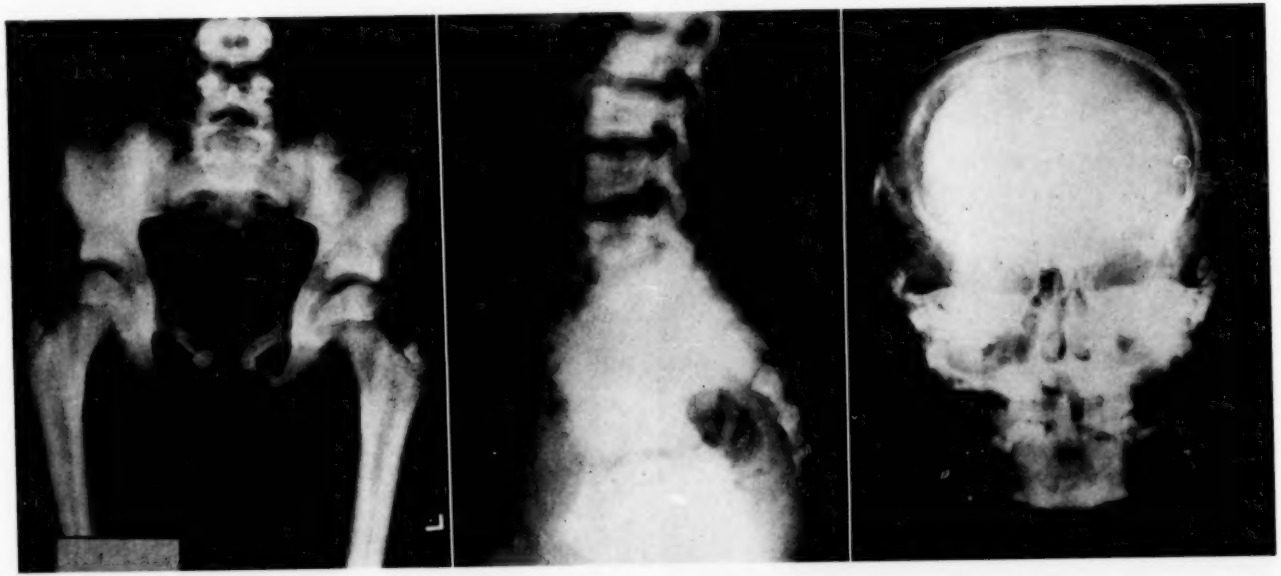

Fig. 3. Fig. 4. Fig. 5.

Fig. 3.—Roentgenogram of the lumbosacral spine, pelvis, and upper femurs shows increased density and marked increased thickness of the cortex of femurs. Father and brother of L. C. show similar changes.

Fig. 4.—Lateral view of lumbosacral spine reveals marked increased density of bone.

Fig. 5.—Roentgenogram of the skull shows increased density, especially over the petrous portion of the temporal bone.

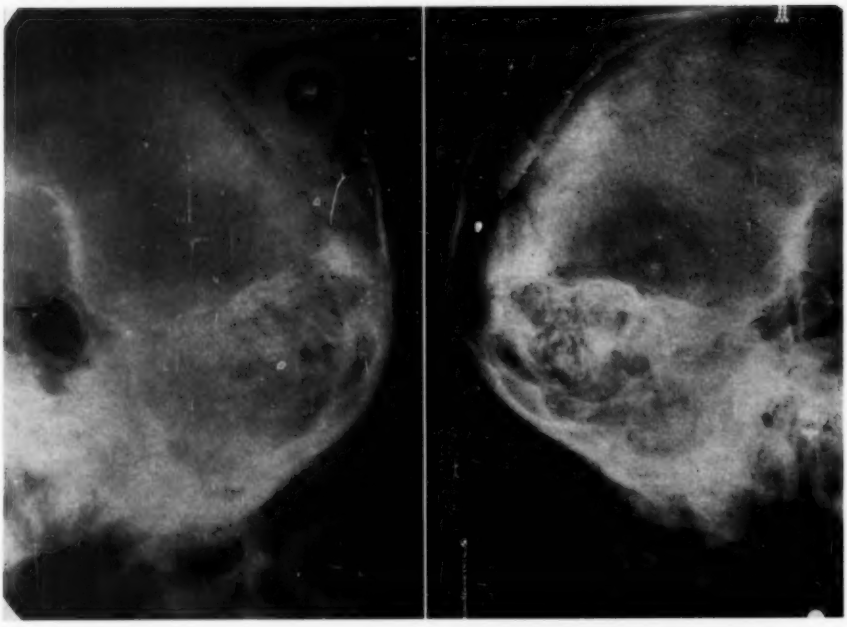

Fig. 6. Fig. 7.

Fig. 6.—Right mastoid region reveals encroachment on the seventh nerve at the stylomastoid foramen.

Fig. 7.—Roentgenogram of the left mastoid region shows clear stylomastoid foramen.

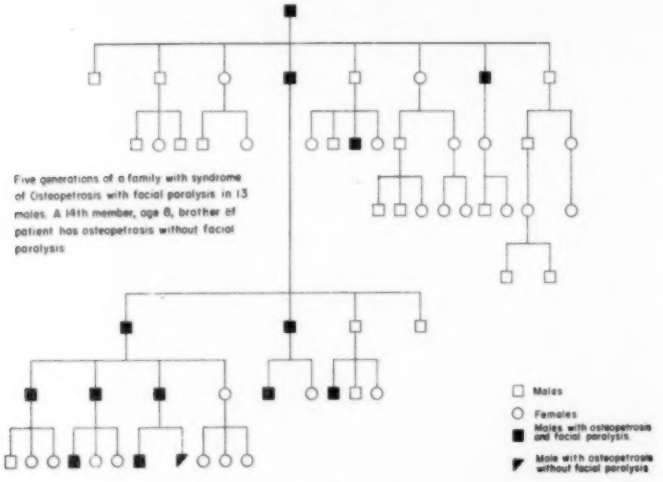
Five generations of a family with syndrome of Osteopetrosis with facial paralysis in 13 males. A 14th member, age 8, brother of patient has osteopetrosis without facial paralysis
Males
Females
Males with osteopetrosis and facial paralysis
Male with osteopetrosis without facial paralysis

Fig. 8.

formation. There is decreased formation of osteoclasts and osteoblasts.[7] Osseous tissue encroaches on the marrow spaces. The total marrow spaces are decreased, and the marrow may undergo fibrous changes. The cortex of the bones shows increased thickness. As a result of these changes, there is frequently an overgrowth of bone in the region of the foramina of the skull which may cause constriction of the cranial nerves. Clublike thickening of the posterior clinoid process and narrowing of the sella turcica are frequently observed in patients with marble bones.

DISCUSSION

The family history indicated that the age of onset of facial paralysis in the 13 cases was approximately 12 years. A possible explanation for this consistent age of onset may be that alternating bands of greater or lesser intensity are present in the diaphysis of the long bones in cases of osteopetrosis. These bands demonstrate that the disease is relatively intermittent and undergoes fluctuation in the rate of growth and intensity.[7] One might assume, therefore, that similar fluctuations in growth and intensity may occur in the skull bones and that at about 12 years of age an increase in bone formation occurred in the petrous portion of the temporal bone to produce encroachment on the seventh cranial nerve in the region of the stylomastoid foramen. There is no evidence that there are any changes in body chemistry in persons with osteopetrosis.

The complications which may occur in osteopetrosis include impairment of vision and blindness as a result of optic atrophy caused by a narrowing of the optic foramina. Deafness due to the encroachment on the auditory nerve has been reported.[7] Narrowing of the cranial foramina has been found at autopsy in a few instances, but until recently it has never been demonstrated by roentgenography. Other reported complications related to osteopetrosis are fractures, hydrocephalus, nystagmus, aplastic anemia, and myelogenous pseudoleukemia.[5]

Osteopetrosis was first described by Albers-Schoenberg in 1904.[1] Since that time, approximately 100 cases have been reported. Most of the reports have been isolated cases, but McPeak[2] reported 8 cases occurring in 3 generations of the same family, 5 in females and 3 in males. This was the largest number of previously reported cases of Marble Bones occurring in one family. Osteopetrosis is usually diagnosed during childhood. The disease may begin in intrauterine life and be fully developed at the time of birth. The etiology is unknown.

A review of the literature pertaining to seventh nerve paralysis, per se, indicates there may be a strong predisposition in some families to develop Bell's palsy. Arkwright[8] reported 4 cases in one family, all of which were due to neuritis. Neuman[9] in 1887 recorded the family histories of 37 cases of facial paralysis. In 24 instances of these he found pronounced nervous disorders. Charcot reported 5 cases of facial paralysis in 3 generations of the same family. None of these reported cases of Bell's palsy contained any reference that

facial paralysis might be caused by pressure on the facial nerve due to abnormal bone growth.

SUMMARY

A syndrome of facial paralysis with osteopetrosis is reported in a boy who developed facial paralysis at 11 years of age. He was one of 13 males in 5 generations of the same family, all of whom developed the facial paralysis at about the same age.

Roentgenographic evidence of bony encroachment on the seventh nerve in the region of the stylomastoid foramen was shown.

It is suggested that when the underlying cause of facial paralysis in a child seems obscure, osteopetrosis be considered and explored as a possible etiologic factor.

The kind suggestions and assistance of Dr. Heyworth Sanford, Dr. Douglas Buchanan, and Dr. A. Arnold in the preparation of this paper are greatly appreciated.

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ABDUCENS NERVE PALSY IN DILANTIN INTOXICATION

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FOR the symptomatic treatment of convulsive disorders, Merritt and Putnam, in 1936, introduced sodium diphenylhydantoin or Dilantin Sodium, a white microcrystalline odorless powder which can be taken for prolonged periods of time either per os or parenterally.[13-17]

The symptoms of Dilantin intoxication are predominantly manifestations of the central nervous system such as ataxia, tremors, nystagmus, diplopia, amblyopia, ptosis, vertigo, nausea and vomiting, slurring of speech, ocular pain, hypotonia, and areflexia. At times fatigue, insomnia, apathy, confusion, delusions, hallucinations, and even psychotic manifestations are seen.[2, 5-7, 9, 19, 23, 26]

The main purpose of this report is to cite two cases of Dilantin intoxication in which the patients suffered marked abducens nerve palsy in conjunction with cerebellar symptoms which have not been reported in the literature.

CASE REPORTS

CASE 1.—J. B., 18-month-old white boy weighing 22 pounds, was admitted to this hospital December 18, 1956. The chief complaints were unsteadiness and deviation of the eyes toward the midline which had begun three days previously. The patient's illness started one week prior to admission with an elevated temperature associated with gradual and progressive deviation of the eyes toward the midline, drowsiness, weakness, and unsteadiness, with a tendency to fall to the right side. The patient was a normal full-term infant at delivery without any evidence of abnormality. He had occasional colds and fevers of short duration and had an episode of generalized convulsions associated with an upper respiratory infection at the age of 6 months. He rapidly fully recovered from this and developed normally thereafter.

On physical examination the patient appeared to be well developed and nourished with no elevation of temperature. Vital signs were normal and, with the exception of mild drowsiness, the rest of the physical examination was normal.

The neurologic examination revealed the following positive findings: There were complete bilateral abducens nerve palsies with obvious convergent strabismus, the fundi were clear without evidence of venous engorgement or papilledema, and the rest of the cranial nerves were entirely normal. There was generalized weakness, marked truncal ataxia associated with moderate hypotonia of all the extremities, and inability to stand. All sensory modalities were normal; the deep tendon reflexes were equal though slightly depressed. No pathologic reflexes were noted.

Laboratory examination revealed the following: Urinalysis and complete blood counts were normal. Serology was negative; nonprotein nitrogen, 24 mg. per cent; fasting blood sugar, 73 mg. per cent. Spinal fluid

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was clear and contained no cells. The protein content was 10 mg. per cent; the sugar, 70 mg. per cent; and the chloride, 114 mEq. per liter. Roentgenograms of skull and chest were normal.

With a presumptive diagnosis of a posterior fossa lesion, further organic studies were carried out. On December 20 the patient was taken to the operating room where posterior bi-parietal trephines and ventriculography were performed with entirely negative results; no evidence of an expanding lesion or increased intracranial pressure was noted. The patient was brought back to the ward for observation.

Further extensive inquiries were made. It was learned that following the patient's convulsion, at the age of 6 months, the family physician gave medications which the parents thought were for the fever and cold. These were given for approximately one week and discontinued. One week prior to admission when the patient developed a rise in temperature, the parents had the prescription refilled without consulting the family physician. Inquiry from the druggist who refilled the prescription revealed that the medication was Dilantin suspension with a concentration of 75 mg. per teaspoonful; the parents had given the patient 1 teaspoonful every 3 hours around the clock for 3 days, thinking all the time that this was a medication for fever. It was now obvious that the patient had Dilantin intoxication.

The patient was put on bed rest without medication and 10 days later, after an uneventful recovery, the bilateral abducens nerve palsies, the convergent strabismus, and all the cerebellar symptoms cleared completely. The patient was discharged on December 20, 1956, in good condition.

CASE 2.—R. L., a 6-year-old white boy, was admitted to this hospital on August 17, 1940, with the chief complaints of drowsiness and staggering gait of one month's duration. The patient had been an epileptic since the age of 2 years, having generalized convulsive seizures two to three times a week, and in some instances once a month. He was given Luminal, 30 mg. 3 times a day, without apparent relief. Two months prior to admission his medication was changed to Dilantin Sodium, 50 mg. 3 times a day, as the Luminal did not seem to control his seizures. One month prior to admission the patient gradually developed drowsiness, apathy, dysarthria, slurring of his speech, and later developed jargon, aphasia, dysphasia, epistaxis, nystagmus, diplopia, truncal ataxia, tremors, dysmetria, hypotonia of muscles, areflexia, and inability to walk.

On admission the vital signs were normal. Physical and neurologic examinations revealed the following positive findings: The pupils were markedly dilated but reacted to light; there was horizontal nystagmus bilaterally on lateral gaze; an abducens nerve palsy was noted on the right. There was no venous engorgement or papilledema of the fundi, and the remaining cranial nerves were normal. He was dysarthric with a slurring tone of the voice. All sensory modalities were intact. The muscles were all hypotonic, and the deep tendon reflexes were entirely absent. There was gross truncal ataxia, dysmetria in all extremities, inability to walk, and on standing the patient fell backwards. The rest of the general physical and neurologic examinations were normal.

Laboratory data revealed the following: Routine urinalysis and complete blood count were normal; serology was negative. Spinal fluid was clear and contained no cells. The protein content was 24 mg. per cent; the sugar, 40 mg. per cent; and the chloride, 112 mEq. per liter. Roentgenograms of the skull and chest were all normal.

During his hospitalization, the patient's medication was discontinued and bed rest was instituted. Surprisingly enough he did not have a single seizure and on the nineth hospital day he became mentally alert and

all of his neurologic symptoms disappeared. He was discharged on the sixteenth hospital day in good condition and entirely free of the symptoms of Dilantin intoxication.

COMMENT

The two patients whose case histories were presented exhibited brain-stem and cerebellar symptoms, the symptoms that first ensue in practically all cases of Dilantin intoxication, particularly in the acute ones. Various other systems may also be affected, namely, the gastrointestinal, hepatobiliary, integumentary, and the reticuloendothelial systems, which constitute a variety of reactions such as hepatitis, lymphadenopathy, exfoliative dermatitis, megaloblastic anemia, aplastic anemia, peripheral neuritis, hirsutism, and increase in libido.[3, 6, 8, 11, 12, 20, 21]

How this variety of manifestations during Dilantin intoxication is brought about is largely unknown and still open for speculation, particularly in regard to the mechanism and pharmacologic action on the central nervous system.

Some authors believe that the main action of Dilantin in the central nervous system is to elevate the threshold for seizures and to prevent the spread of seizures. These effects are thought to be operative even in acute hyponatremia and with cortisone and thyroxin therapy where the seizure threshold is abnormally lowered.[4, 27, 28]

Further observations have revealed that Dilantin readily passes the blood-brain barrier system despite its slow absorption in the intestinal tract: it has been found in the brain, liver, and fat in its highest concentration when it reaches its maximum plasma level and in the heart, spleen, kidneys, lungs, skeletal muscles, and red blood cells in progressively lower concentrations. Its route of elimination is primarily through the liver where it is partly detoxified and through the kidney where 1 to 4 per cent is eliminated unchanged.[2, 24, 25]

Review of the literature regarding Dilantin's quantitative concentration in the various parts of the brain failed to reveal any such study. However, it has recently been shown that animals given toxic doses of the drug developed degeneration of the cerebellum, with a reduction in the number of Purkinje cells. To cite an example, there is a patient at this hospital who has been on Dilantin for the past 20 years and who for several years has been suffering from brain-stem and cerebellar manifestations for which, after extensive investigation, posterior fossa exploration with cerebellar biopsies was carried out. These revealed marked cerebellar atrophy, with degeneration to almost complete abolition of the Purkinje cells of the cerebellum.

With the predominance of brain-stem and cerebellar symptoms in Dilantin intoxication, it may be inferred that most likely there is a difference in its quantitative accumulation in the different structures of the brain and that it may have a selective affinity for such parts. Certain other drugs, such as streptomycin (eighth nerve), methyl alcohol, and curare, when given in physiologic or toxic doses, have special affinity for specific structures in the brain or elsewhere.

The two cases reported suggest that Dilantin might have a special affinity for the abducens nerve or nucleus. This is a mere speculation and certainly warrants further investigation.

One important attribute of Dilantin, however, despite the variety of its toxic manifestations, is that the toxic incidence is quite low and its prevention and treatment are simple discontinuation of the drug. It is still considered one of the best anticonvulsants in the treatment of symptomatic convulsive disorders as it has an apparent superiority over its contemporaries, the barbiturates and bromides; it is nonsedative, non-habit forming, and its efficacy in controlling psychomotor seizures certainly merits its use.[1, 10, 13, 18, 22]

SUMMARY

Two unusual cases of Dilantin intoxication with abducens nerve palsy and cerebellar symptoms have been reported. The mechanism and pharmacologic action of Dilantin upon the central nervous system is largely unknown. Simple discontinuation of the drug during intoxication is highly stressed in its prevention and treatment.

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"The great work of national education in this country, which dates from the passing of Mr. Foster's Act in 1870, has had the effect of calling widespread attention to the excessive demands made by schools and teachers upon children. . . ."

"Teachers, as a body, do not understand the physiological and psychological natures of children; and until they do, there will always be the twofold danger of attempting too much, or of attempting it in the wrong way and by the wrong means. . . . "

"The physician recognizes in this severe ordeal grave danger to the brain and nervous system of growing children, by which the mind is narrowed, the character weakened, and disease invited. Headache is one of the first and most persistent consequences of this baneful practice."

William Henry Day, M.D., from Some Observations on Headaches in Children, and Their Relation to Mental Training, 1887.

SPONTANEOUS INTRAPERITONEAL RUPTURE OF PYONEPHROTIC KIDNEY IN INFANCY

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SPONTANEOUS intraperitoneal rupture of a pyonephrotic kidney is extremely rare; only a few cases have been reported, all of which apparently were in adults.

CASE REPORT

C. G., a French Canadian girl, was admitted to Ottawa General Hospital on May 30, 1958, at the age of 27 days. She weighed 8 pounds. She had had a high fever for 2 days, associated with abdominal distension, vomiting, and constipation.

Physical examination revealed a well-hydrated, alert, and nontoxic infant. Her temperature was 101.4° F. (rectal); pulse, 180; respiration, 38; and blood pressure, 80/50. The abdomen was grossly distended, tense, and tympanitic. There was no abnormal peristalsis or ascites, and the bowel sounds were audible. An apparently cystic mass was barely palpable in the left renal region. Otherwise the examination was unremarkable.

The roentgenologic examination suggested intestinal obstruction. Clinically, the possibility of hydronephrosis was considered. The urinalysis revealed a few pus cells, but the culture was sterile.

The infant's condition improved temporarily on conservative treatment, but on the third hospital day she developed diarrhea and appeared toxic. The abdomen became grossly distended because of free fluid in the peritoneal cavity as evidenced by radiologic examination. No bowel sounds were audible. The leukocyte count was 50,000 per cubic millimeter, with 70 per cent polymorphonuclear cells which contained toxic granulations. The blood urea nitrogen was 42 mg. per cent.

A laparotomy revealed slightly turbid fluid in the peritoneal cavity and inflammation and adhesions of the small bowel. Pyonephrosis of the left kidney was demonstrated. There was a perforation in the pelvic area of about 1 cm. in diameter (Fig. 1). By palpation, the right kidney seemed to be normal in size. The left ureter was dilated and appeared to be obstructed at the bladder neck. A smaller accessory ureter was also present (Fig. 1). Because of rapid deterioration in the general condition, surgical manipulation was reduced to a minimum, anterior renal drainage was established, and penicillin, streptomycin, Chloromycetin, and Mandelamine were prescribed.

Subsequently, urine and stool cultures grew *Klebsiella* and *Aerobacter aerogenes* which were only moderately sensitive to Chloromycetin and tetracycline and resistant to most of the other antibiotics. The clinical course was unfavorable despite several plasma and blood transfusions, and the blood urea nitrogen rose to 50 mg. per cent. A nephrectomy was performed 24 days after the rupture of the pyonephrotic kidney. The infant expired a few hours later.

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Autopsy revealed minimal interstitial pneumonitis and an organizing peritonitis. The lumen of the accessory ureter was obliterated.

DISCUSSION

The cause of the spontaneous rupture of the pyonephrotic kidney, which apparently occurred on the third day of admission, is not clear. In pyonephrosis or hydronephrosis the renal tissue, the calyces, and the pelvis may be reduced to the thinness of paper, but perforation rarely occurs. In the infant described here there was evidence of peritoneal inflammation which involved the intestines and caused intermittent obstruction. The resistance of the bacteria to antibiotics was a deterrant in combating the infection.

So far as can be ascertained, only 10 instances of spontaneous perforation of a hydro- or pyonephrotic kidney have been recorded, all of which were in adults.[1-4] Couvelaire[2] referred to the cases reported by Michel and Artaud, Hubener, Sauerbruch, Martins, Rost, and Hammel.

SUMMARY

Spontaneous intraperitoneal rupture of a pyonephrotic kidney in an infant, 27 days of age, is reported. Only 10 instances of similar perforations have been recorded; none of them were in infants.

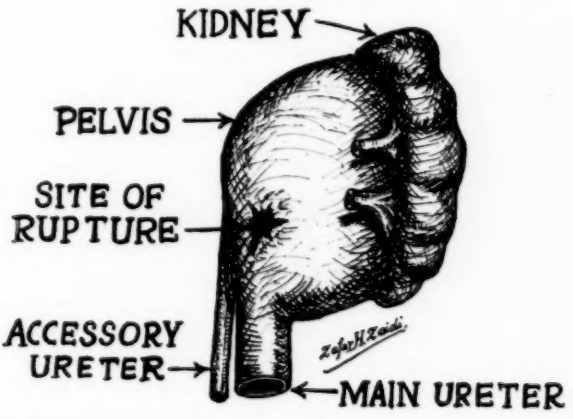

Fig. 1.—Diagrammatic representation of the left kidney showing the perforation in the grossly distended pelvis of the kidney. The main ureter is also distended; the accessory ureter was apparently atretic.

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ORAL PHYTONADIONE IN NEONATAL HYPOPROTHROMBINEMIA

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DURING the last decade the status of plasma prothrombin in the newborn infant has been reinvestigated, especially in regard to the importance of vitamin K. Observations in several laboratories indicate that infants have slightly depressed levels of plasma prothrombin and of the stable factor (also known as Factor VII) on their first day of life[1-4] and that both components fall progressively over the following three or four days, returning to normal levels by the seventh to the tenth day of life.[1-7] In approximately one out of two hundred infants this hypoprothrombinemia is severe enough to cause overt bleeding, so-called "hemorrhagic disease of the newborn infant."[4] One suspected cause for the deficiencies of prothrombin and of the stable factor is a deficiency of vitamin K[1-3, 7-9]; administration of this vitamin to the infant on the first day of life has been reported to prevent these deficiencies in most instances.[9]

In 1955, Allison[10] reported the occurrence of kernicterus and hemolytic anemia in premature infants whose only therapy had been relatively high doses of a water-soluble vitamin K analogue. Other authors substantiated the dangers of parenterally administered vitamin K analogues in doses of from 10 to 50 mg., especially to the premature infant. The situation was deemed sufficiently serious that Severinghaus,[15] in letters to three pediatric journals, called attention to the potentially harmful effects of high doses of the water-soluble analogues of vitamin K when administered parenterally. The Council on Drugs of the American Medical Association then felt it necessary to recommend as a maximum limit for a single dose an equivalent of 1 mg. of synthetic vitamin K (menadione) as adequate to prevent hemorrhagic disease in the newborn infant. This corresponds to a dose of 3 mg. of menadiol sodium diphosphate (Synkavite Sodium Diphosphate, vitamin K analogue).[16]

The naturally existing form of vitamin K is an oil-soluble liquid, phytonadione or vitamin K_1. Phytonadione has been found superior to the synthetic water-soluble vitamin K, especially as an antidote to all types of prothrombopenic-inducing anticoagulants.[10] Its potency is such that Alexander[18] recommends its use over the synthetic water-soluble forms in all situations where vitamin K is required. This laboratory has previously demonstrated that the oral administration of phytonadione to adults is as effective as the usually recommended intravenously administered emulsified preparation.[19] In view of this experience our laboratory felt that a further study comparing the effectiveness of orally administered phytonadione to

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parenterally administered water-soluble vitamin K in the newborn infant would be of interest. To date, there has been no report of oral administration of phytonadione to the newborn infant, except for a casual mention of the successful use of a close analogue, vitamin K_1 oxide, in two newborn infants with severe hypoprothrombinemia.[1] To facilitate this study, a new micromethod[20] for the bedside determination of the capillary blood prothrombin time was developed.

Method and Materials.—Our capillary tube technique for the determination of whole blood prothrombin utilizes a clean glass capillary tube which measures 1 ml. in internal diameter and 3 cm. in length. This tube is marked off in 1 cm. intervals. A mixture of 0.0125 M Calcium Chloride and thromboplastin solution* is drawn up to the second centimeter mark and then *freely flowing* blood, as obtained from a deep skin puncture in a digital tuft, ear lobe, or heel, is drawn to the third centimeter mark. The tube is then immediately grasped between the thumb and forefinger to close off the system and inverted repeatedly until the end point of a definite precipitate is reached. The timing of the test begins from the time of the mixing of the blood in the tube to this definite and easily visible end point of obvious precipitation. It must be strongly emphasized again that the capillary blood must flow freely. Any squeezing or local trauma, no matter how trivial, that may be felt necessary to speed such a flow of blood will create marked variations and inaccuracies in the timing. If the blood flow is too slow and inadequate for use, a new site should be punctured.

*Solu-Plastin is manufactured by Schieffelin & Co., 16-30 Cooper Square, New York 3, N. Y.

The infants studied were born on the ward service of the Beth Israel Hospital in Newark, New Jersey. These infants were born of mothers who were followed in our clinics at least through the last trimester of pregnancy and given adequate dietary instruction as well as the usual supplementary multivitamins, which did not contain vitamin K.

All of these newborn infants were studied by daily duplicate prothrombin determinations throughout their entire nursery stay. The first test was obtained in all but 11 infants within the first 24 hours of life. It is our nursery procedure at present to administer 2.5 mg. of menadiol sodium diphosphate intramuscularly on the day of birth. A group of 23 infants treated in such fashion was studied with daily prothrombin times for the duration of their hospital stay. A second group of 16 infants was given 2 mg. of phytonadione orally in a dextrose feeding on the first day of life. This mixture was prepared by diluting 1 ml. of an emulsified preparation of phytonadione* containing 50 mg. in 49 ml. of 5 per cent dextrose. Two milliliters of this preparation, which contain 2 mg. of phytonadione, were added to a standard dextrose formula. A third control group of 52 infants was not given any vitamin K and their prothrombin times were observed daily from birth. After some initial experience, it was determined that times higher than 25 seconds were potentially unsafe and required therapy to prevent the possibility of bleeding. Fifteen infants had such prothrombin times; 11 of them were given 2 mg. of

*Mephyton is manufactured by Merck Sharp & Dohme. Division of Merck & Co., Philadelphia 1, Pa.

TABLE I. CHANGES IN CAPILLARY BLOOD PROTHROMBIN TIMES IN INFANTS GIVEN PARENTERAL MENADIONE OR ORAL PHYTONADIONE ON THE FIRST DAY OF LIFE

	CONTROL					PARENTERAL MENADIONE					ORAL PHYTONADIONE				
Days of life	1	2	3	4	5	1	2	3	4	5	6	1	2	3	4	5
Number studied	52	50	45	44	14	14	19	23	23	8	6	14	16	16	16	3
Mean prothrombin time in seconds	20	19	19	18	19	20	19	18	17	17	17	18	17	17	17	16
Standard deviation from the mean in seconds	4	6	3	2	2	4	3	2	2	2	1	3	1	2	2	1

phytonadione orally. The medication was uniformly accepted without difficulty.

Results.—Table I summarizes the results of the comparison studies between the parenterally administered water-soluble vitamin K analogue and the orally administered phytonadione. Considering the variation observed with such a biologic determination (as demonstrated by the statistical calculation of the standard deviation from the mean), there is no statistical difference in the mean daily prothrombin times observed with the two modes of therapy. Orally administered natural vitamin K was as efficient in producing normal levels of prothrombin time and maintaining such levels as the parenterally administered water-soluble analogue. When considering the untreated group of 52 newborn infants, we were impressed by the large number of infants, nearly one third of the total, who were found to have elevated prothrombin times. These prothrombin times ranged from 25 to 35 seconds for the most part, but one infant was born with a 45 second prothrombin time and another with a 52 second one Eight infants of this group had abnormal elevations on the

TABLE II. THE RESPONSE OF THE HYPOPROTHROMBINEMIC (MORE THAN TWENTY-FIVE SECONDS PROTHROMBIN TIME) NEONATAL INFANT TO TWO MILLIGRAMS OF ORAL PHYTONADIONE.*

Days after treatment	0	1	2	3	4
Number studied	9	6	9	9	3
Mean prothrombin time in seconds	>25	20	19	18	18
Standard deviation from the mean in seconds		3	3	1	1

*All of these infants were treated within the first three days of life.

second or third day of life. As shown in Table II, all of the infants who received orally administered phytonadione had normal prothrombin times within 24 hours, which remained in the normal range in the succeeding days. No untoward reaction to either vitamin K form was observed.

DISCUSSION

In the newborn infant phytonadione can be successfully substituted for the potentially toxic menadione sodium biphosphate in the usual clinical situation in which the parenteral form is commonly administered: (1) Its prophylactic administration on the first day of life is effective in preventing a vitamin K deficient type of hypoprothrombinemia. (2) It is effective in the treatment of vitamin K deficient hypoprothrombinemia. The ease of administration of phytonadione in a routine feeding makes it the method of choice. Thus, there would seem to be little place for the parenteral injection of menadione sodium biphosphate for the newborn infant, except in the rare situation when the infant is unable to swallow or digest. Further experience, however, will be necessary to confirm the safety of the orally administered vitamin K_1. Since this vitamin is the form found in nature and usually assimilated by infant and adult, it would seem unlikely that any difficulty would be experienced with a single dose of 2 mg. The high incidence of hypoprothrombinemia in our series, however mild in degree, confirms the need for a nontoxic yet potent form of vitamin K prophylaxis for the first week of life. Orally administered phytonadione appears to be ideal for such a purpose.

SUMMARY

Orally administered phytonadione in doses of 2 mg. of an emulsion given in a dextrose feeding formula on the first day of life is as effective as menadiol sodium biphosphate given intramuscularly in doses of 2.5 mg. in preventing abnormal elevations of the prothrombin time during the first five neonatal days. This same dose of phytonadione rapidly and effectively reduced to normal limits the abnormally high prothrombin times of 9 of a control group of 52 newborn infants who had not received any form of vitamin K.

We are indebted to Miss Elsie Grunwald for her laboratory assistance.

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THE PLACENTA

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TRADITIONALLY the assignment of the infant to the obstetrician or the pediatrician is decided solely on whether or not he has completely emerged from the birth canal. However, the problems that beset the newborn infant are not so simply divided and much is lost to all concerned by the rigid application of this classification. In recent years there has been a growing realization among both obstetricians and pediatricians that this division must be bridged. It is a reflection of this new awareness that an article devoted to the placenta is given space in a pediatric journal.

It is impossible to cover in detail a subject that has invited so much work and thought. It will be sufficient if this review manages to present a coherent story of the current concepts of the placenta, one that will be of interest and possibly of use to the pediatrician. The bibliography will be largely limited to the recent and more inclusive publications, those that will most conveniently provide an entree to the literature for the interested reader. The pleasure of giving credit to the original workers will therefore frequently be foregone in the interests of simplicity.

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COMPARATIVE PLACENTATION

In most primitive animal forms the continuation of the species requires enormous fertility. Although masses of eggs are produced and cast out, only a relatively few survive. With progress up the evolutionary tree, many species began to provide greater protection to the eggs, increasing their chances for survival and permitting a reduction in the energy devoted to reproduction. This trend took a new form and greater efficiency when the fertilized egg was retained in the mother and discharged only after a period of development.

Ovoviparity represented the simplest modification of this type. The retained egg derived its nourishment from the yolk deposited in the egg. Thus, the newborn contained only as much nitrogen, carbon, or salts as are present in the fertilized egg. In a later evolutionary development uterine secretions (uterine milk) were produced which could be used by the embryo as a source of nourishment. Correspondingly less yolk had to be deposited in the egg. Finally the placenta evolved, bringing the maternal and fetal circulations into close approximation and permitting considerable exchange of materials between the two. This important innovation was attained by some fishes and reptiles.[1]

With the evolution of mammals, we find the placenta a well-developed organ, though varying considerably in detail among the several species. The most durable attempt so far to classify the mammalian placenta has been that of Grosser (Fig. 1), which is based on the number of tissue layers intervening between the maternal and fetal circulations. Grosser attempted to extend this anatomical description to a functional interpretation, implying that the placenta with the thinnest barrier would provide the freest interchange of materials. The implication of greater efficiency for some placentas was readily attacked when it was pointed out that even an epitheliochorial placenta is capable of producing a horse! Recently Grosser's classification has come under a barrage of criticism on more technical grounds.[2] The classification has been found anatomically too simple for so complex an organ. For example, the human placenta which is classified as hemochorial is actually epitheliochorial in the early stages of gestation. And the sow's placenta which is epitheliochorial has many areas where the maternal and fetal circulations come into very close apposition.

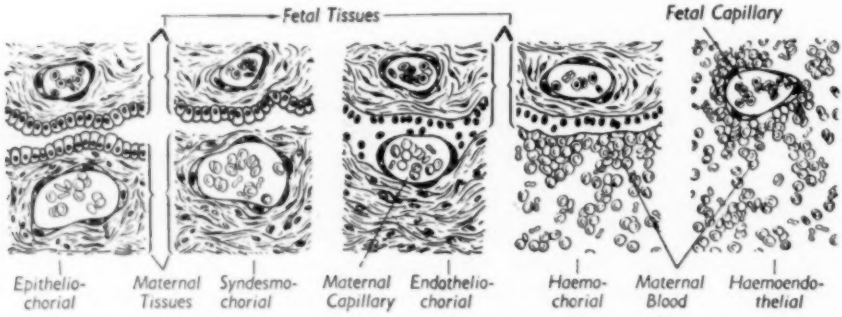

Fig. 1.—Grosser's classification of placenta according to thickness of barrier between maternal and fetal circulations.

Epitheliochorial	Syndesmochorial	Endotheliochorial	Hemochorial	Hemoendothelial
pig horse	sheep cow	cat dog	man monkey	rat, rabbit guinea pig

(From Amoroso, E. C.: Placentation, *in* Marshall's Physiology of Reproduction, edited by A. S. Parkes, New York, 1952, Longmans, Green & Co.)

There has also been criticism of the attempt to translate the anatomical feature of thickness of membrane to a functional concept of ease of permeability. This can be misleading. A recent example of this concerns the transfer of antibodies from mother to fetus. In the animals with a hemochorial-type placenta antibodies are frequently found in high titer in the newborn animal and this has been attributed to transfer across the "thin" placenta. However, Brambell and associates[22] have demonstrated that in many of these animals transfer does not occur across the allantoic placenta at all but across a fetal membrane called the splanchnopleure.

We will return to Brambell's work later in a more appropriate place. The points to be made here are that classifications tend to oversimplify, that there are many subtle as well as gross differences among placentas of the various species, and that it is hazardous to transfer observations made in one species to another without subjecting them to test.

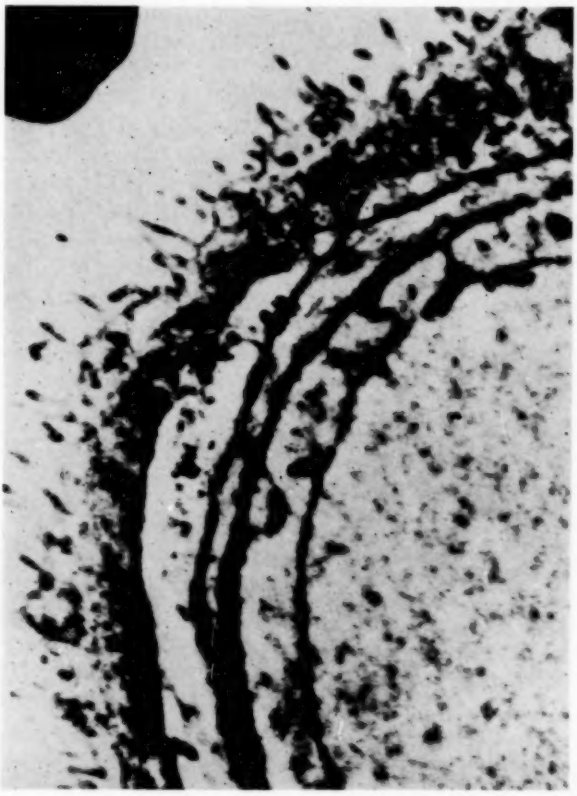

Fig. 2.—Section of human villus at term as seen through an electronmicroscope (×15,000). From upper left corner to lower right are maternal red cell, syncytium with microvilli, two basement membranes, and endothelium of fetal capillary. (From Dempsey, E.: Transactions of First Conference on Gestation, March 9 to 11, 1954, New York, Josiah Macy, Jr., Foundation, p. 204.)

The Human Placenta.[1]—A brief description of human placentation may be of value to those who have not been recently exposed to the subject.

As early as the second week after implantation, villi have formed from the trophoblast (chorionic epithelium) and by the third week a mesodermal core carrying blood vessels has grown into the villi. At first the villi surround the developing embryo, but subsequent development takes place only in the basal area forming the placenta, and the rest of the villi

degenerate. By continuous branching and invasion of the decidua (endometrium), the placenta increases in size and complexity. Erosion of maternal vessels produces small pools of blood which coalesce to form the maternal lake or intervillous space.

Coincident with the increasing number of villi, there is an increasing vascularity within the villi bringing the blood vessels closer to the epithelium, and thus closer to the maternal circulation. The epithelium also becomes progressively thinner. During the first trimester there is a well-marked double layer, the inner layer of Langhans (cytotrophoblast) and the outer syncytial layer. The outer syncytial layer is believed to arise from the Langhans' cells. As pregnancy advances, the Langhans' layer almost completely disappears and the syncytial layer becomes extremely thin in many areas.

And so, at term, the placenta consists of innumerable richly vascularized fetal villi dipping into a maternal lake of blood (the intervillous space) and presenting an enormous surface, estimated at 10 square meters for exchange of materials. Only a very thin membrane is interposed between th two circulations. Terminally there is a deposition of eosinophilic-staining material (fibrinoid) in the villi which reduces to some extent the area of exchange. The details of the anatomy and physiology of the circulation are extremely complex and are still the subject of intense research and debate.[3]

ENDOCRINE FUNCTION

The placenta is certainly the largest endocrine organ, and it ranks next to the pituitary in versatility. The endocrine functions of the placenta that have been established with any certainty are directly concerned with the maintenance of pregnancy. The extent to which the placenta has superseded other endocrine organs in this respect varies greatly among the species. This section of the review will be limited to the primate placenta, particularly the human. A broader review will shortly become available to the interested reader.[4]

We shall also exclude from consideration the extensive literature concerned with histochemistry and the extraction of endocrines from the placenta. Studies of this kind are often suggestive and indicate the direction for further work. However, histochemistry seldom provides sufficiently accurate identification of the materials under study; and extraction procedures cannot differentiate a site of storage from one of synthesis.

There is good evidence that the placenta is the site of synthesis of at least three hormones: chorionic gonadotrophin, estrogens, and progesterone.

The curve of *gonadotrophic activity* in the urine during pregnancy parallels in time the development and the waning of the Langhans' layer of the placenta (Fig. 3). Gonadotrophic activity has been reported in the urine of a male with a chorioepithelioma.[6] More direct evidence has been provided by tissue transplants. The Langhans' cells will survive and grow for months in tissue culture and gonadotrophic activity can be demonstrated in the culture medium.[7] The human placenta has also been transplanted to the anterior chamber

of a rabbit's eye. Gonadotrophic activity could be demonstrated in the recipient for months despite hypophysectomy.[8]

nation of pregnancy, indicating a source other than the ovary.[10]

Transplant studies again provided more direct evidence. Tissue culture

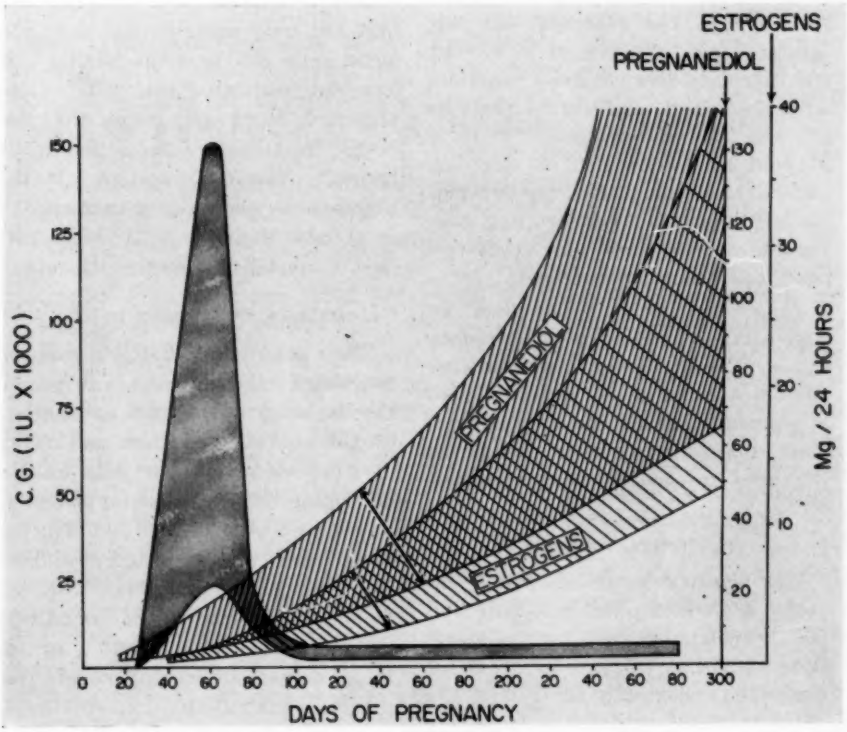

Fig. 3.—Normal range of urinary excretion of hormone metabolites during pregnancy. Chorionic gonadotrophin (dark shaded area) in international units. (Modified from Venning, E. H.: Excretion of Various Hormone Metabolites in Normal Pregnancy, Obst. & Gynec. Serv. 32: 661, 1948.)

The evidence for a placental origin of *estrogens* and *progesterone* is also partly circumstantial and partly direct. Oophorectomy in the human after the second or third month of gestation does not interrupt pregnancy, although it is generally accepted that both steroids are required for the maintenance of pregnancy. The urinary excretion of the metabolites of these steroids (Fig. 3) was uninterrupted until the termi-

was unsuccessful because the syncytial cells, which are probably the site of synthesis of these steroids, did not survive. However, estrogenic activity could be demonstrated in oophorectemized rabbits bearing intraocular transplants of human placenta.[8]

The recent great strides in the steroid field have been sparked by the replacement of bioassay methods, by more specific chemical identification,

and by the investigation of individual enzymatic steps in the metabolic pathways. These methods have been applied to the placenta in a limited way so far. Ryan[12] has demonstrated that the placenta can unsaturate the 'A' ring of a steroid and therefore does not need materials with preformed unsaturated rings in the synthesis of estrogens. There is a rapid interconversion of estradiol and estrone, with a tendency to reach an equilibrium.[13] The in vitro conversion of cholesterol to progesterone[14] has been demonstrated.

There is, at the present time, no convincing evidence that the placenta can synthesize *adrenal hormones* or adrenal-stimulating hormones. There is considerable circumstantial evidence that is provocative, indicating the need for more research in this area.

PLACENTAL TRANSFER

The primary function of the placenta is to bring the maternal and fetal circulations into close juxtaposition to permit efficient exchange of materials. Originally the role of the placenta was considered to be purely passive, presenting a sievelike obstruction which permitted transfer of small materials like crystalloids and barring the larger such as proteins. It was a reasonable conclusion based on the available experimental techniques and concepts of transfer. However, this image of a simple passive role for the placenta is rapidly yielding to a complex and poorly understood one in which the placenta selectively controls the rates of transfer of a wide variety of materials.

Another major modification in our concept of placental transfer concerns the efficiency with which materials are excluded. Thirty years ago it was doubted that proteins could pass the placenta. Now more refined techniques have demonstrated that not only proteins but even red blood cells can pass the barrier. It has been estimated that 0.03 ml. of maternal blood may cross the placenta from mother to fetus in 24 hours.[66] The old question "Is the placenta permeable to x substance?" must now yield to "At what rate does x substance cross the placenta?"

OXYGEN AND CARBON DIOXIDE

The most immediately essential function of the placenta is to permit the exchange of oxygen and carbon dioxide between mother and fetus, to serve as an efficient lung for the developing embryo. The approach to this aspect of placental function has been beset with unusually difficult technical problems. The basic information relating to the transfer of oxygen and carbon dioxide in the intact subject under physiologic conditions has been impossible to achieve. The anatomically secure position of fetus and placenta prevents direct approach, and any intervention may drastically alter the conditions of transfer.

One group of investigators has considered the fetus to be profoundly anoxemic with umbilical vein oxygen saturations falling from 80 per cent at 35 weeks' in the human to 65 per cent at term.[15] Other investigators have attributed these low levels to artefacts, the use of anesthesia, the supine position of the subject with pressure of the fetus on the pelvic

vessels, handling the umbilical vessels, etc. By modifying these techniques in the sheep Dawes obtained figures of oxygen saturations of 80 per cent in the umbilical vein, a level that was maintained until term.[3] Furthermore, slowing the rate of flow in the umbilical circulation did not increase the oxygen saturation. This would suggest that the blood is completely oxygenated on its passage through the placenta but that roughly one fifth of the blood passes through "shunts" and is not exposed to oxygenation at all. The presence of shunts has been suggested by anatomical studies.[16]

It has not been possible to repeat these experiments in the human, and none of the figures that are currently available were collected under conditions that can be considered representative of the intrauterine state. However, anatomical considerations indicate that the fetus exists in utero under conditions that are anoxemic by post-partum standards. Even if the figures obtained in the sheep were to apply to the human, only about one half of the fetal blood passes through the placenta at each circuit. Thus, the 80 per cent saturation in the umbilical vein would be reduced to close to 60 per cent before the blood reaches the fetal tissues because of mixture with venous blood from the rest of the animal.

The acid-base balance is to a large extent dependent on the transfer of carbon dioxide. The difficulties with investigation in this area are of the same nature and related to those of oxygen exchange. The induction of severe acidosis in the pregnant rabbit will induce similar changes in the fetus.[17] However, it may take hours for a new equilibrium to be reached because of the relatively slow movement of certain ions.

PROTEINS

Maternal plasma *amino acids* rapidly cross the placenta and are incorporated into fetal proteins.[18] This is the major source of fetal protein throughout most, if not all, of pregnancy. There appears to be a specific transport mechanism in the placenta which maintains the amino acid concentration on the fetal side higher than on the maternal side. Active transport mechanisms are commonly stereospecific, and it has been demonstrated that the natural (l-) amino acids are transferred across the placenta far more efficiently than the d-form.[19] Competition among amino acids[20] and a "saturation" effect with increasing maternal amino acid concentration[21] have also been demonstrated. As with carbohydrates, the handling of amino acids by the placental membrane and by many cell membranes present striking similarities, suggesting similar mechanisms.

Knowledge concerning transfer of *plasma proteins* was for a long time limited to antibodies. Until the advent of isotopic techniques, this was the only way of labeling proteins so that their pathway could be followed. It was known that maternal antibodies appeared in good concentration in the fetal circulation in many species including the human. With the aid of plasma proteins tagged with radioactive isotopes, it has now been shown that the fetal gamma globulin fraction is entirely or almost entirely derived from the mother.[18] Significant amounts of fetal albumin and possibly

other of the plasma globulins are also interchanged with maternal plasma proteins.

The *rate of transfer of proteins* is considerably slower than for amino acids, and it seems to vary among the proteins. The relatively slow utilization rates (turnover times) of certain of the plasma proteins, for example, albumin and gamma globulin, makes it possible to supply a significant proportion of the fetal requirements in this manner. The very short turnover time of many of the other globulins makes it unlikely that fetal requirements can be met by transfer of maternal proteins.

The *route of transfer* of antibodies had always been assumed to be transplacental until Brambell and his colleagues[22] in a logically formulated series of experiments showed this not true in the rabbit and guinea pig. In these animals transfer occurs across a modified yolk sac, one of the fetal membranes. Brambell and coworkers then extended these observations to demonstrate that in

TABLE I. COMPARISON OF ANTIBODY TITERS IN MOTHER AND FETUS

ANTIBODY	TITERS		
	ABOUT EQUAL	CONSIDERABLY LOWER IN FETUS	NOT DEMONSTRABLE IN FETUS
Isonagglutinins			
anti-A, anti-B		+	
anti-Rh agglutinins			+
anti-Rh conglutinins	+		
Antitoxins			
diphtheria	+		
tetanus	+		
scarlet fever	+		
Antibacterial antibodies			
pertussis	+		
influenza bacillus		+	
dysentery		+	
typhoid fever "H"	+		
typhoid fever "O"			+
colon bacillus "H" and "O"			+
Antivirus antibodies			
measles	+		
herpes simplex	+		
poliomyelitis	+		
encephalitis, Japanese B	+		
vaccinia	+		
Complement-fixing antibodies			
influenza	+		
parotitis	+		
syphilis		+	
toxoplasmosis	+		
Hemolysins			
sheep erythrocytes		+	
Antihemolysins			
antistreptolysin	+		
antistaphylolysin	+		
Allergens			
"skin-sensitizing"			+
"blocking"		+	
Miscellaneous			
C-reactive protein			+
bacteriostatic activity		+	
rickettsia	+		

From Vahlquist, B.: The Transfer of Antibodies From Mother to Offspring, Advances Pediat. **10**: 305, 1958.

many species transfer occurred across an entodermal lining, either gut or yolk sac, and suggested that this may also be true of the human. However, recent observations in the monkey[23] with radioactive proteins and in the human with radioactive proteins and antibodies[24] indicate that the primate is the exception in that transfer of plasma proteins takes place across the allantoic placenta.

large molecules, but it will probably require a chemical interpretation to explain the specificity of the process.

The *synthesis* of proteins, other than cell proteins, by the placenta has not been adequately investigated. The evidence for a chorionic gonadotrophin is good. On indirect evidence investigators have suggested that the placenta might synthesize serum albumin and gamma globulin.

TABLE II. RELATIVE LEVELS OF SOME CONSTITUENTS OF MATERNAL AND CORD BLOOD IN THE HUMAN

		ABOUT EQUAL	LOWER IN FETUS	HIGHER IN FETUS
Amino acid	N			+
Urea	N	+		
Uric acid	N	+		
Creatine	N	+		
Creatinine	N	+		
Inorganic	P			+
Lipoid	P		+	
Total fatty	acids		+	
Cholesterol			+	
Glucose			+	
Lactic acid				+
Calcium				+
Magnesium		+		
Chloride		+		
Sodium		+		
Potassium				+*

From Needham, J.: Chemical Embryology 3: 1531, New York, 1931, The Macmillan Co.
*A more recent study using flame photometry revealed levels close to the normal adult range.[62]

The mechanism by which these large molecules are transferred across the placenta must be complex and specific. Thus, homologous and heterologous plasma proteins are transferred at different rates in a manner that cannot be explained by molecular size, and the same seems to be true among the several homologous plasma proteins (Table I). Electron-microscopists have suggested that transfer of materials of such large size occurs by pinocytosis[25]: the engulfing of materials by an active cell border and then its passage through the cell in vacuoles. This gives a structural model for the transfer of

Direct investigation by tissue incubations has failed to substantiate this possibility.[26] A case of pregnancy in an agammaglobulinemic woman has provided strong circumstantial evidence that the placenta can under these remarkable circumstances synthesize antibody.[27] A new approach to this problem is strongly indicated.

Fetal *nucleic acids* appear to be synthesized by the fetus and are not derived intact from the mother.[28]

The blood levels of the major *nitrogenous waste products,* urea and uric acid, are the same in maternal and fetal blood, and it is assumed that they travel freely across the placenta

in both directions (Table II). Transfer of urea from mother to fetus has been demonstrated[29] and the reverse is likely but remains to be proved. However, equilibration takes hours. Because of this, an abrupt elevation in maternal urea may not be reflected in the newborn infant. An interesting observation is that the placenta can synthesize urea from ammonium chloride.[30] This is done more efficiently near term than early in pregnancy.

CARBOHYDRATES

Carbohydrates are probably the main source of energy for the developing fetus and, as might be expected, pass readily through the placenta. It was assumed by early investigators that this was a simple process of diffusion because there was a correlation with molecular weight (monosaccharides could penetrate but disaccharides could not) and because changes in the maternal level were paralleled by changes in the fetal level.

Recently accumulated evidence makes it very unlikely that transfer is simply passive. Fructose, which is the same molecular weight as glucose, crosses the placenta much more slowly,[33] and the guinea pig placenta will transport D-xylose at three times the rate of L-xylose.[34] Such stereospecificity commonly involves enzymatic activity. The infusion of another carbohydrate (sorbose) into the mother will depress the transfer of glucose,[35] indicating competition for a transport mechanism. An analysis of the kinetics in the sheep also conforms with a transport mechanism.[36]

These observations parallel those made in reference to carbohydrate transport across other membranes. Here, as elsewhere, the actual nature of the transport mechanism is not known, but it may be suspected that a solution of the problem in one area will lead to quick understanding elsewhere.

LIPIDS

The origin of fetal lipids has also been approached with the aid of isotopes and with the same general conclusions as indicated for proteins.[31] The fetus is capable of efficiently synthesizing its own lipids from small molecules such as acetate derived from the mother. A small fraction of the fetal fatty acids appear to arrive intact from the mother. Phospholipids and cholesterol are poorly transported across the placenta. However, as Villee[32] has pointed out, the transfer of neutral fats across the placenta has not yet been studied, though this is known to occur across the intestine.

ELECTROLYTES

Flexner and his associates[37] have studied the transfer of *sodium* across the placenta in a series of animals, including man. Radioactive sodium was injected into the maternal circulation and the rate of appearance of radioactivity in the fetus was taken as indication of the rate of transfer of sodium. In Fig. 4 are presented the results of his investigations in the human. The increasing rate of transfer during the first nine tenths of gestation was attributed to increasing numbers of villi with improved vascularization in the placenta. The fall-off in the last few weeks of pregnancy was attributed to thrombi and hyaline changes. This last observation, to

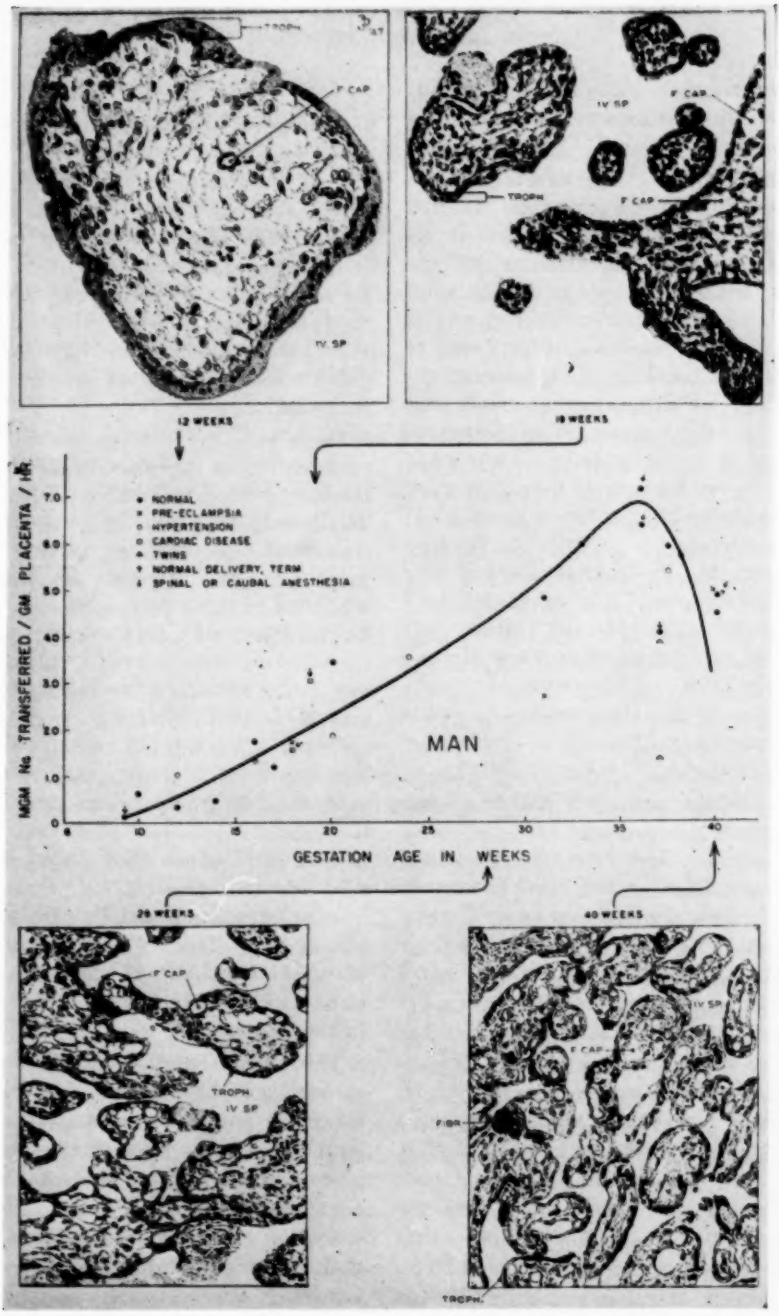

Fig. 4.—The transfer of sodium across the placenta in the human compared to the histologic picture of the placenta. (From Flexner, L. B., Cowie, D. B., Hellman, L. M., Wilde, W. S., and Vosburgh, G. J.: Permeability of Human Placenta to Sodium in Normal and Abnormal Pregnancies and Supply of Sodium to Human Fetus as Determined With Radioactive Sodium, Am. J. Obst. & Gynec. 55: 469, 1948.)

which we shall refer again, is a point that has been stressed recently by clinicians.

In Flexner's experiments there is actually no detectable net transfer of sodium because the sodium levels on both sides of the placenta are usually equal. The transfer of radioactive sodium across the placenta is balanced by the transfer of a similar amount of sodium in the opposite direction. Flexner has assumed that this technique measures the net transfer that would actually take place if there were no reverse flow of sodium, a condition that is never approached physiologically. Critics have suggested that the isotopic method may only measure "interchange" and have no relation to net transfer. It is not possible at the present time to settle this controversy, but the changes in transfer rates in the course of pregnancy remain an interesting observation.

A similar approach has been used to study the transfer of *phosphorus* and *iron*. The inorganic phosphate concentration in the fetal plasma in the guinea pig averages twice the maternal, indicating active transfer from mother to fetus against a gradient.[38] Nothing is known about the transport mechanism. The transfer of iron has been studied in the rabbit.[39] It appears to be a one-way transfer from mother to fetus. This is reminiscent of the circumstances in the intestine, and the presence of ferritin in both placenta and intestine increases the similarity. Once again it appears that basic transport mechanisms may be reproduced at different membrane barriers and that solving the problem at one may solve the problem at all.

VITAMINS

Experimentally induced vitamin deficiencies[40] and excesses[41] in the diet of pregnant animals have produced congenital anomalies in the young. The magnitude of the stress in each instance was severe, and so far no counterpart in human experience has been reported. Infants have been born with evidence of vitamin deficiencies reflecting an inadequate antenatal supply.[69, 70]

There is a gross difference in the transfer across the placenta of lipid-soluble and water-soluble vitamins. The former are found in low concentration in cord blood, suggesting the poor transport typical of lipids, while the water-soluble vitamins are frequently in higher concentration than in maternal blood. This generalization is true of the lipid-soluble vitamins A[42] and E.[43] Analytical methods have limited our information concerning vitamin D. Warkany[44] has demonstrated in rats that a rachitogenic diet given to the mother will induce bony abnormalities and that this can be prevented by supplementation with D. However, this gives no direct information about placental transport of the vitamins. Congenital rickets has been reported in the human.[68, 69]

Thiamine,[45] B_{12},[46] riboflavin,[47] and ascorbic acid[48] are all found in higher concentration in cord blood than in maternal blood. Since transfer takes place from the lower maternal concentration to the higher fetal concentration, a transport mechanism other than passive diffusion must be assumed. More refined analytical methods have suggested a mechanism for two of these vitamins.

Lust and his co-workers[47] have found that the riboflavin circulating in maternal plasma is primarily in the form of flavin adenine dinucleotide, while that in the fetal plasma is the free riboflavin. It would appear that the placenta must be relatively impermeable to both. In vitro studies demonstrated that placental tissue could convert the maternal type to the fetal and might thereby facilitate transfer.

Ascorbic acid exists in the blood as dehydro-ascorbic acid and L-ascorbic acid. Räihä[49] found that the vitamin C level determined as dehydro-ascorbic acid was about equal in human maternal and fetal blood but that the total ascorbic acid level was higher in the fetus. He demonstrated in guinea pigs that dehydro-ascorbic acid could cross the placenta from mother to fetus but L-ascorbic acid could not. This suggests that the former may cross to the fetus and then be converted by the fetus to the impermeable form which would then accumulate in high concentration.

ENDOCRINE TRANSFER

A standard approach to the problem of placental transfer of endocrines has been to determine the physiologic effect on the mother or fetus of the removal of endocrine organs in either party or to determine the effect of supplying an excess of hormones, usually to the mother. The complex endocrine interrelations of pregnancy makes it difficult to evaluate many of these experiments. In general, it is believed that the protein hormones do not cross the placenta in sufficient quantities to be physiologically effective. However, definitive data are largely lacking.

Observations on chorionic gonadotrophin are of particular interest. In the human the level in maternal blood is considerably higher than in fetal tissue[50] or in cord blood.[51] The data suggest that chorionic gonadotrophin which is synthesized in the placenta finds its way more readily into the maternal circulation.

Better analytical methods and the availability of radioactive tracers have increased our information concerning the nonprotein hormones. The human placenta is permeable to radioactive thyroxine and triiodothyronine.[52] The clinical observation that cretins may be born already stigmatized indicates that at least in some cases the transfer of these maternal hormones does not keep pace with fetal requirements. Steroids appear to cross the placenta with facility. This is true of hydrocortisone[53] and of estrogens.[54] The placenta is much more permeable to the "free" or lipid-soluble form of estrogens than to the water-soluble glucuronides. This suggests an advantage to the fetus in its inability to form glucuronides. If the fetus were to conjugate estrogens efficiently, the glucuronides might tend to accumulate in the fetus. It remains to be seen whether this observation may be generalized to other lipid-soluble materials such as bilirubin.

PATHOLOGY

With the complete dependence of the fetus on the placenta and with the complexity of functions that the placenta must perform, it is fairly

certain that many fetal problems have their origin in placental dysfunction. However, this remains a relatively unexplored area with only the gross abnormalities recognized.

The *premature separations* of the placenta are serious and obscure obstetrical problems. The repercussions on the fetus are well known and are largely secondary to anoxia and occasionally anemia from hemorrhage. A newly recognized complication of premature separation which has stimulated interest is hypofibrinogenemia. The hypofibrinogenemia has been attributed by some investigators to the release of fibrinolytic substances from the placenta.[56] An alternative or possibly complementary explanation is that the release of thromboplastin from the placenta produces an excessive deposition of fibrin with depletion of the circulating blood.[55] The disturbance in coagulation appears to be limited to the mother.

Anemia in the infant which is present at birth has been attributed to intrauterine bleeding. In the absence of external hemorrhage it has been assumed that there is rupture of a fetal vessel into the maternal circulation. The higher pressure in the fetal circulation results in flow of blood from fetus to mother. On occasion it has been possible to confirm the diagnosis by identifying fetal blood in the maternal circulation.[57]

Postmaturity (dysmaturity, placental dysfunction) has attracted considerable attention since it was realized that fetal mortality rose with prolonged gestation.[58] The clinical picture has been well described in the pediatric literature and need not be repeated here. The concept of reduced placental efficiency toward term has received support from Flexner's data on sodium transfer (Fig. 4). Reduction in oxygen saturation in cord blood in prolonged pregnancy has also been reported[59] but these data have been criticized as previously discussed. The indicated treatment is obviously cesarean section, but the problem is how to select those cases that require intervention. There are crude clinical guides but what is needed is a test of placental function to help in this difficult decision.

There is evidence for reduced placental function in *eclampsia* which may explain the complications encountered in the infant. The transfer of sodium, antipyrine,[60] and possibly oxygen are reduced.[15] The evidence implicating the placenta as a primary factor in the cause of eclampsia has increased. Experimental nephritis has been produced in rats by injecting an antiserum prepared against rat placenta.[61] This suggests a common antigen in the two organs and a mechanism to explain the renal lesions in eclampsia. Circulating antibodies have been reported in the blood of women with eclampsias to an antigen extracted from the human placenta.[62] These studies must be confirmed and extended.

CONCLUSION

Interest in placental research is rapidly growing. The recent conferences on the subject give testimony to this. We may look forward to a rapid increase in our knowledge in the near future. On the one hand there is an accumulation of knowledge and disciplines that have been obtained in other fields which may

be applied with benefit to the placenta. Basic mechanisms of transport worked out by membrane physiologists on frog skin or everted intestine or elsewhere will undoubtedly be found applicable to the placental membrane. Also, as a corollary, research workers interested in fundamental mechanisms are being attracted to the placenta because of the unique advantages offered by this organ. Page[63] has catalogued an impressive array of enzymes already found in the placenta, and Villee and Gordon[64] and Talalay and Williams-Ashman[65] have found it a useful organ to elucidate the relation of estrogens to oxidative metabolism. With the blossoming of interest in the problem of the homotransplant, we may expect intensive investigation of a remarkably successful homotransplant, the placenta. It is not too much to hope that with the increase in basic information of the physiology of the placenta will come a better understanding of placental pathology.

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Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, *Editor*
John M. Craig, *Assistant Editor*

THIS was the first Children's Medical Center admission of this 2-year-old white boy, who was apparently well until three weeks prior to admission when, along with his twin and four other siblings, he developed chickenpox. The disease was considered to be mild, and he did well until five days prior to admission when he ate poorly and "didn't seem to be his usual self." The following day he vomited four times and slept an unusual length of time during the day. It was noted that he did not use his hands as well as usual and that he walked "very gingerly," with very small steps. He was not thought to have had fever. He continued to vomit three to five times a day but had normal bowel movements.

The patient weighed 4 pounds at birth, but the prenatal history was otherwise unremarkable. He developed normally and had no behavior difficulties.

On admission to The Children's Medical Center his vital signs were: temperature, 98.6° F., pulse, 138, and respirations, 24 per minute. The height and weight were below the third percentile for his age. The fontanels were closed, and the skull measured 49.8 cm. in circumference. He was lethargic but irritable and resented being disturbed. The pupils were dilated but reacted to light. The fundi were normal, with no elevation of the disks. The deep tendon reflexes were normal in character. The remainder of the neurologic examination was negative. The only other positive findings were the presence of a few healing lesions of chickenpox on the scalp and a few fresh petechial hemorrhages on the neck.

The initial laboratory examinations revealed a hemoglobin of 10.0 Gm. per cent and a white blood cell count of 6,800 per cubic millimeter. The differential count revealed that there was 64 per cent polymorphonuclear leukocytes. On smear the erythrocytes displayed stippling and slight anisocytosis and poikilocytosis. The urine contained traces of albumin and sugar, but the sediment was negative. A qualitative test for urinary coproporphyrin gave a trace reaction. The ferric chloride test for phenylpyruvic acid was negative. The lumbar puncture fluid contained 1 monocyte per cubic millimeter, a

normal sugar level, and 122 mg. per cent of protein; no pressure was recorded.

The patient was treated symptomatically, without change in the clinical condition for the first 48 hours. On the third hospital day he developed fever, followed a few hours later by convulsion which began in the right arm and leg, and later spread to the opposite side of the body. A repeat lumbar puncture revealed normal pressure and unchanged chemical values.

He remained unconscious, with variable neurologic signs. During the afternoon he became rigid and developed gasping respirations which were followed by apnea and death.

DR. RANDOLPH K. BYERS.*—There are many points in the history that suggest a cerebral disorder. These include repeated vomiting, alterations in personality, dullness of intellect, drowsiness, and poor coordination of the hands. The physical findings also indicate a primary central nervous system disorder, with display of both lethargy and irritability, hyperactive deep reflexes, and ankle clonus. In children with involvement of the cerebrospinal tract the Babinski reflex usually becomes abnormal before clonus appears, but one sign may be positive in the absence of the other.

The laboratory data reveal several findings of importance which, while not specific for lead posioning, are suggestive. These include the presence of stippled erythrocytes, the presence of a trace of coproporphyrin in the urine, and the increased protein with no increase in cells in the spinal fluid. The latter finding is also seen in obstruction of the subarachnoid space or during the recovery phase of inflammatory processes, but there the protein would probably not be as high as in this case.

This, then, is a child who has an acute diffuse bilateral disease process in his brain. Since his illness began with an infection, we might commence our discussion by a consideration of this possibility. In the first place, we may consider it to be due to visible infectious agents; one should not forget syphilis, since we saw two patients with central nervous system lues in the past winter. It does not seem likely that the infection in this case is caused by a bacterium, protozoon, or other visible agent.

Among the viral agents, we have seen in the past winter several children who had had encephalitis following an attack of Asian influenza, with rises in antibody titer; one of these had an encephalitis which was very similar to the von Economo type seen in the 1920's with oculogyric crises. The onset in May in this child is early for equine encephalitis because the usual arthropod vector is not present then. The lack of pleocytosis would tend to rule out lymphocytic choriomeningitis (a benign infection), mumps, and herpes simplex. Rabies may be responsible for a high spinal fluid protein with few cells but the peripheral blood counts are higher.

The acute disseminated encephalopathies of unknown origin that follow measles, chickenpox, vaccinal inoculation, rabies prophylaxis, which are probably a sensitivity phenomenon, must be considered because of

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the onset, after an exanthematous disease, within the 3 weeks' delay period seen in such illness. What is against this diagnosis? Most such children have fever at the time of onset and are very sick, with a high leukocyte count, but the spinal fluid shows little increase in protein and only a few cells, which are usually lymphocytes. The course is very acute, terminating in either death or complete recovery. Another variety of encephalitis, without a known etiology, is acute hemorrhagic encephalitis. We might consider cerebral purpura which is thought to be due to sensitization of the blood vessels, or (as it occurs) in a more fulminant form of acute necrotizing hemorrhagic encephalitis, with development of massive hemorrhages into the cerebral white matter and dissolution of the blood vessels. These present quite a different clinical and spinal fluid picture, however.

Acute toxic encephalitis, which occurs concurrently with infections such as measles, chickenpox, pneumonia, or influenza may have a quite sudden onset, with loss of consciousness, greatly increased intracranial pressure, and death within 12 to 36 hours. Such children usually have a normal spinal fluid protein and at autopsy have a wet and swollen brain.

The cerebral leukodystrophies, chiefly with white matter degeneration, may have a rather sudden onset and be accompanied by an increase in the cerebrospinal fluid protein. Although Schilder's disease may not be symmetrical in distribution, metachromatic leukodystrophy usually is so. I would think the other laboratory findings would lead me away from consideration of these.

The polioencephalitides such as the lipidoses have a much more gradual onset than is seen in this child. The metabolic disturbances giving rise to an encephalitic picture such as anoxia, hypoglycemia, adrenal insufficiency with hypotension, water and sodium intoxication must be considered. This boy has had vomiting but not enough to have given rise to any important change in his serum sodium level.

Acute poisoning such as that due to strychnine, belladonna, giving rise to convulsions, or the barbiturates causing coma may be discerned by the course of events.

Of the chronic poisons, of which I believe this is an example, there is good evidence, especially for lead. We may enumerate the important data: first, his age is right; second, he became ill in the late spring, a time when the disease frequently begins; third, he had persistent vomiting which, although the time of day is not stated here, usually occurs chiefly before breakfast; fourth, he had unsteadiness of gait; fifth, infection is a common precipitating agent because there may be an accompanying change in the blood pH which will free stored lead triphosphate from the bone and make it available as diphosphate to the soft tissues, this may be further aggravated by the acidosis following persistent vomiting; sixth, as previously mentioned, the changes in the spinal fluid, while not specific, are quite consistent with lead poisoning, namely, an increase in protein but only a minimal change in cells. The anemia is the type seen in lead poisoning and the coproporphyrinuria also fits. Against the diagnosis is the report of a normal spinal fluid pressure. Since no definite measurement is given, I will assume that no manometric test was done and that an estimate of the flow

of spinal fluid was made through the needle, but this may be misleading if the needle is not accurately within the subarachnoid space.

I conclude that this boy died from lead poisoning. Had a diagnosis been made promptly, we would have had 48 hours in which to give Versene, to which he should have responded.

DR. CRAIG.—How soon will a person respond to Versene? Is it a matter of hours?

DR. BYERS.—The response to Versene takes from 48 to 72 hours in most instances. We began to worry about this a few months ago when we got daily spinal fluids from a child whose intestine contained flakes of lead paint by roentgenographic study. When he was put on Versene, his spinal fluid protein initially was around 60, rising to 80 the second day, to 112 the third day, and coming down again after that. This suggested that perhaps this latent period was due in part to the fact that the Versene in circulation reached the intestine in sufficient quantities to enhance further absorption of lead. Lead Versenate is slightly dissociable in the body, so that some of the lead is available to the soft tissue. Recently we have been removing the lead from the bowel by enemas before starting Versene treatment. In one serial lumbar puncture study with such treatment protein levels began to fall directly without the preliminary rise.

DR. CRAIG.—What about the clinical response? Here is a child who became comatose after his convulsion. Would you expect a dramatic comeback with administration of Versene?

DR. BYERS.—I think that after the convulsion, it was too late. He might have responded if he had been promptly decompressed by craniotomy. We have a child with lead poisoning on the ward now who was brought in after convulsions and in coma. Dr. Shillito took off most of the parietal parts of the skull on both sides. The patient is not very well yet, but she is responding slightly. She has also been in shock, with a blood pressure of 40. This presents another problem, because if the lead is made soluble by Versene so that it can be excreted through the kidneys and if the latter are not functioning, the lead Versenate piles up in the blood and may reach a level toxic for the renal tubules. This girl has now begun to form urine, but we will withold Versene until an adequate excretion has been established.

DR. SHERWIN KEVY.—Why did this child have such a long latent period after his acute febrile illness?

DR. BYERS.—The proportion of lead present as diphosphate increases rapidly in serum whenever pH goes much below 7.45; at pH 7.35 this becomes appreciable. It is believed that the diphosphate is the toxic ion for the brain in lead encephalopathy. With acidosis or also alkalosis, one gets an increase in the relatively serum-soluble diphosphate and a consequent redistribution of the lead from the stores in the bone to the brain, liver, and kidney, so that children who vomit with an infection may suddenly increase their vomiting and quite rapidly go into coma.

DR. CRAIG.—In some places they are pursuing craniotomy decompressions

vigorously. Dr. McLaurin, in Cincinnati, has done some seven or so in a year.[1] We have done comparatively few decompressions here, haven't we?

DR. BYERS.—In the 3 years between 1952 and 1955 we did two, and in the 3 years before that we did only one.

DR. CRAIG.—Has continuous spinal drainage been abandoned?

DR. BYERS.—It is still being done. As far as I am concerned, it seems very unlikely to do much good, because at autopsy in these acute cases the ventricles are collapsed and there is little spinal fluid to drain. You might gain 5 to 10 c.c. of space, but most of that in the spinal cord rather than in the cerebrum.

DR. MARTIN H. WITTENBORG.—This child showed no real signs of increased intracranial pressure. His fontanels were closed and no eye-ground changes were seen, though his symptoms appear obvious.

DR. BYERS.—I don't know why that is. I can remember a girl with a cerebellar tumor who when a needle was placed in the ventricle had fluid shoot right up to the roof of the operating room, yet she had flat optic discs, though she did have some separation of her cranial sutures.

DR. LOUIS K. DIAMOND.—What would be your indication for surgical decompression, Dr. Byers? One wouldn't wait for convulsions, since they are late signs.

DR. BYERS.—No, I wouldn't wait for convulsions. However, since the signs of increased pressure were not present here, I don't think you would have decompressed this child before the convulsions.

DR. DIAMOND.—Yet, because we did not measure the lumbar fluid pressure and because the edema is intracellular, not an intercellular or external edema, we may not get a large amount of fluid shooting out on lumbar puncture, but if we measure the pressure, we might detect some increased pressure.

DR. BYERS.—I think you would have found increased pressure with a manometer, but I would say that in this child the spinal fluid observations were probably due to the fact that the needle did not communicate freely with the subarachnoid space.

DR. CRAIG.—Dr. Diamond, this child has stipple cells. Some people report abnormalities of the early erythroblasts: polyploidy, abnormalities of mitotic activity, etc. Have you seen any of this in bone marrow?

DR. DIAMOND.—I am not familiar with that. I think that stippling which is not found in a patient in the presence of a known hemoglobinopathy, like the Mediterranean anemia, should be considered diagnostic of lead poisoning, until proved otherwise. Where many stipple cells are present, they practically make a diagnosis of lead poisoning.

DR. CRAIG.—What is the ultimate prognosis of a child who has required a surgical decompression for acute lead poisoning?

DR. BYERS.—Well, we have a few with good results; one patient, now 21 or 22 years of age, has dull normal intelligence. There is another child who had had a decompression 3 years ago who looked quite retarded for the first year or so afterward, but who recovered and now, after 3

years, scores quite normally on psychologic examination. There are two others who are feeble-minded and who were probably not feeble-minded before their disease. I have seen several other of the older patients before the days of Versene treatment who have not become very well-organized people. I think that since the advent of Versene, we have done perhaps a little better than before.

DR. DIAMOND.—Do you consider the onset of convulsions a bad prognostic sign?

DR. BYERS.—Yes, once the patient starts having convulsions, death usually occurs within a short period. However, there was a child here in 1955 who had a convulsion in one hospital in July and was discharged with the diagnosis of encephalitis. She then went to another hospital, had another convulsion about a week or two later, and then went to a third hospital. She became a patient here after she had been having convulsions for a month. She responded very well to Versene, without any decompression. She was probably at the borderline of convulsions during this period. She is now very feeble-minded.

Of the 45 cases that we have treated here with Versene in the last 3 years, 17 had what I thought of as acute lead encephalitis, and of those, about 8 or 9 are seriously retarded.

DR. DIAMOND.—They did not have convulsions?

DR. BYERS.—They were either comatose or had convulsions. Of these, more than one half are retarded and some of them still have rather specialized defects.

Another thing which is very bad in children with lead poisoning is to let them go home and be re-exposed to lead. The home may be cleaned of lead, but the parents then don't pay their rent, so they are evicted; they then may get a new apartment and the child eats the lead paint there. Another problem is to have a belligerent father who won't allow his house to be investigated. One such family has 3 feeble-minded children as a result of lead poisoning.

DR. CRAIG.—Has the acute mortality rate been altered by the use of Versene?

DR. BYERS.—The acute mortality, I should say, has been very much the same since Versene as before, somewhere around 10 per cent, I believe. I think the eventual prognosis of those that live, in terms of the number of competitive people, has been considerably improved. We do not have a series large enough to make this statistically reliable, but of our 45 cases, I have been able to follow 40 in the past 3 years. Of these, 21 are getting along perfectly well, with normal psychologic examinations. The children of school age are doing satisfactory work in school. Another 6 or 7 children have rather specialized cerebral defects, with difficulties in perception of form and shape, and they have difficulty in learning to read or write when they get to school. Some of these recover and become competent, again, with time. Approximately 10 or 12 of the whole group are obviously grossly feeble-minded and won't recover.

DR. WITTENBORG.—Can you have a lead encephalopathy with no long-bone roentgenographic signs?

DR. BYERS.—Oh yes, we have had several patients with lead exposures for 5 to 6 weeks who had nothing to show in their long bones at all. It is also true that in late childhood and adult life there may be lead encephalopathy with nothing in the long bones even when the exposure is fairly chronic.

DR. JONATHAN COHEN.—Dr. Byers, is anything known of the site of action of lead diphosphate in the brain?

DR. BYERS.—No, I don't know of anything that has been published which describes destruction of enzymes.

DR. ALBERT FRANK.—How helpful is a flat plate of the abdomen to determine the presence of metal in the intestine?

DR. BYERS.—It hasn't been done in more than one half of the cases, but where it was done within the first 24 hours after admission to the hospital, it was practically always positive. I think that in one instance it showed nothing.

DR. FRANK.—Do you feel that this, in a child, might be the most valuable single roentgenographic examination?

DR. BYERS.—In an emergency it would be a valuable hint but I can show you children with radio-opaque material in the intestine that were stones and other things. One child had so many stones in his colon that he could not stand erect.

DR. CRAIG.—Caffey[2] says that the lead line of the long bones is not specific.

DR. BYERS.—There is no single sign of lead poisoning that can't be mimicked by something else. I think Dr. Diamond's sign of many stipple cells in blood that looks otherwise fairly normal (by laboratory examination) comes nearest to being a reliable sign of acute lead poisoning. However, there is no sign of lead poisoning that hasn't been absent in some of our cases with severe lead poisoning. In the diagnostic files of this hospital I found 65 cases labeled as lead poisoning, of whom 20 were obviously spurious. They had just one x-ray or a stipple cell or a coproporphyrin reaction. One youngster came down with polio the next day, which can cause just as much coproporphyrinuria as lead poisoning.

DR. CRAIG.—After all this, it would be nice if this turned out not to be lead poisoning!

The diagnosis was firmly established by the removal of the bladder urine at autopsy. This contained a little over 1 γ per cubic centimeter of lead. I believe further examinations were done at the patient's home and large amounts of lead were encountered in various areas. There are certain autopsy findings which are fairly specific for lead poisoning, and I think that we could have strongly suggested the diagnosis on histopathologic findings alone. The first of these is the rather marked swelling and prominence of the cells of proximal convoluted tubules. Here they are broader and the mitochondrial pattern is somewhat disturbed but even more characteristic are very large cells, some of them with marked pallor and distortion of the mitochondrial pattern with enlarged nuclei and characteristic intranuclear inclusion bodies, in the loops of Henle. The inclusion bodies are interesting, in some ways, because they will take a Feulgen stain for desoxyribose nucleic

acid. This material is extractable by lipid solvents, even after paraffin embedding from Zenker fixation.[3] It is not known whether or not this is actual altered desoxyribosenucleoprotein. These cells also show an elongation of the cell body which is quite characteristic and occasional degenerative forms are seen. These findings, of course, are associated with the glycosuria, animoaciduria, and phosphaturia. In the vertebra and the ribs there were quite characteristic changes, also, which consist of a zone of mature cellular cartilage matrix which apparently remains with little ingrowth of the blood vessels or normal degeneration of this cartilage mass (Fig. 2). Marsden and Wilson,[4] in Manchester, England, have been able to demonstrate by histochemical stains with lead sulfide the presence of lead here. The brain, too, I think was characteristic; it weighed 25 per cent more than the normal weight and the most easily recognizable changes were in the white matter. These are described in the literature and Marsden describes neuronal changes in his cases. I have never been particularly impressed with these. It always seemed to me that the interstitial tissue and the astrocytic elements and the blood vessels and the white matter suffer more than the other areas. Very markedly swollen astrocytic elements with swollen, prominent, sucker feet and prominence of all the endothelial cells with proliferation and swelling are found (Fig. 3). This change is a very diffuse one.

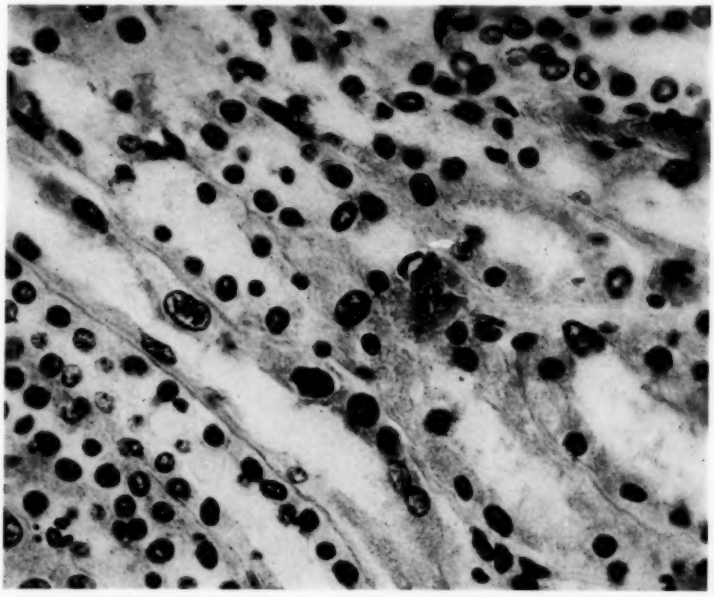

Fig. 1.—Photomicrograph of the kidney. The loops of Henle contain large hyperchromatic nuclei and inclusion bodies. The nuclei of the convoluted tubules are variable in size and often hyperchromatic, while the cytoplasm is swollen and granular. (Hematoxylin and eosin ×600.)

Fig. 2.

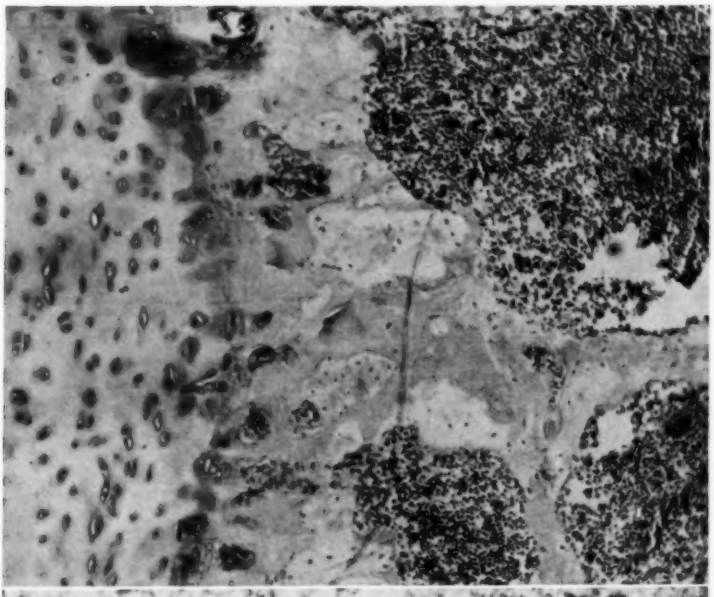

Fig. 3.

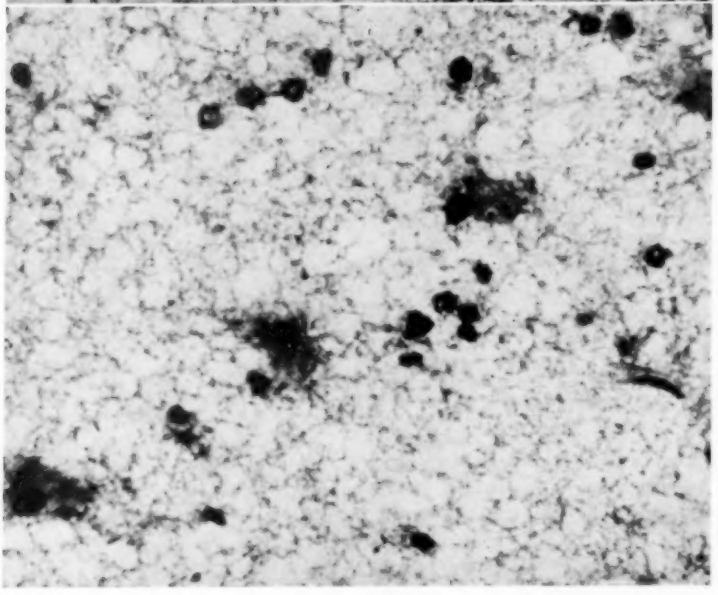

Fig. 2.—Photomicrograph of the vertebrae. There is a broad zone of persisting cartilage matrix (between arrows) with poor cartilage degeneration or vascular penetration. (Hematoxylin and eosin ×145.)

Fig. 3.—Photomicrograph of the brain. The white matter shows separation of the glial net by edema and marked swelling of the astrocytic cell bodies. (Hematoxylin and eosin ×600.)

There are occasional polymorphonuclear cells scattered diffusely throughout the brain substance. We could not demonstrate necrosis or inclusions in the liver cells. The bone marrow was not significantly altered, although, in other cases, we have had a shift to the left and polyploidy of erythroid elements.

I wonder if Dr. Wittenborg or Dr. Byers has ever seen what could be called rickets in these children? This has been reported in the literature because of the increased phosphate and amino acid losses in the urine.

DR. BYERS.—I have read about them in the literature, but I don't ever remember having seen this Fanconi-like syndrome. It has been reported by Chisholm and associates.[5]

Over one half of our cases have their onset in July. The mechanism of this is probably due to three things: first, outdoor paint is more likely to contain lead than indoor paint so that children playing outdoors are exposed to lead more readily. If a child were to eat two or three chips of peeling paint, he could get 40 to 50 ml. of lead in the stool over a 24-hour period. In industry 7 mg. is regarded as extremely hazardous. Second, it has been shown that white rats with 10 per cent lead in their diet while kept indoors have no difficulty, but if you place the rats on the roof, they die in a relatively short time, so that sunshine itself plays a role. Third, in rabbits which have been poisoned with lead administered intraperitoneally, the coproporphyrinuria increases very suddenly if they are exposed to sunlight. Sunshine has something to do with increasing the absorption of lead from the gut, just as it does with calcium, and also probably has something to do with enhancing its deleterious metabolic effects.

DR. CRAIG.—Do you ever see lead neuritis in children?

DR. BYERS.—Yes, we have seen a few cases. It occurs in the children who are exposed more chronically: those who chew well-organized painted surfaces and therefore probably get a smaller dosage of lead at any one time.

DR. CRAIG.—There was a man in England who daubed a board with various substances and put it in front of a child who had pica.[5] The child immediately chose to eat the lead paint in preference to all other substances. The question arose as to whether it was the linseed oil in the paint that attracted the child, since the child tended to prefer fatty substances. In such a test other children have paid no attention to the lead-containing substances.

DR. DIAMOND.—Do you know of a follow-up on this family?

DR. KEVY.—This child and another sibling were exposed to lead. The twin had a slightly delayed developmental history before the lead poisoning episode and is perhaps a little slow. Whether it was because of being a twin or whether it was caused by the lead poisoning, I would not know. The house was repainted.

DR. DIAMOND.—Isn't it true that retarded children develop pica more frequently than normal children?

DR. BYERS.—Yes, the series I referred to contains an excess number

of children who were retarded before the lead poisoning; it is not as large an excess as the literature would indicate, but it certainly is one of the contributing factors. I think 7 out of 46 children were so retarded.

DR. DIAMOND.—Someone has examined the series of lead poisoning cases and pointed out the high percentage of emotional disturbances as a basic factor.

DR. BYERS.—This has been pointed out by a number of people. If a 2-year-old child is put in the back yard or on the back porch, which may be covered with chips of paint, he is bound to eat them, as he will eat anything else. Those children may not have any emotional disturbance. The children who chew on things or who chew the paint off well-preserved painted walls are more likely to be the children with emotional disturbances. Three or 4 children who have been studied were in conflict with their mothers. Someone has also reported a series of 21 cases, 7 or 8 of whom had bitten their mothers severely.

DR. CRAIG.—Why is there so much more lead poisoning in this country than in England, where it is rather uncommon?

DR. DIAMOND.—There is no law against the use of lead house paint on most of our statutes. In England they have laws prohibiting paint companies from putting lead in their product. We could never get it through here because of manufacturers' opposition.

DR. BYERS.—One or two states have passed such laws. New Jersey and Michigan have laws requiring the landlord to repaint the house if a child gets lead poisoning, but you have to prove that the child got lead poisoning there before you can get the house repainted.

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Comments on Current Literature

VIRUS ISOLATION IN FATAL HUMAN CASES OF ASIAN INFLUENZA

OBSERVATIONS concerned with the 1957 pandemic of Asian influenza indicate that, in general case fatality rates were low but that in some instances the course was fulminant; in these cases the disease was comparable to the rapidly lethal variety of influenza associated with the pandemic of 1918 to 1920 and with several smaller epidemics occurring subsequently. Numerous reports dealing with the various aspects of Asian influenza have appeared recently in the medical literature. An unusual study was carried out in Cleveland, Ohio, during the period between September 28 and December 17, 1957. These investigations were prompted by the occurrence of sudden and unexplained death in young persons in the Cleveland area early in October, 1957. Careful autopsies disclosed pathologic findings compatible with fatal influenza. Alerted by these findings, the medical community in Cleveland undertook a cooperative study which has yielded some interesting and important facts concerning our most recent pandemic of influenza. The findings in 33 patients whose death was associated with Asian influenza were investigated thoroughly, an important aspect of the cooperative study being the collection of tissues for virus study.

The initial report of these investigations, which appeared in the February, 1959, issue of the *Proceedings of the Society for Experimental Biology and Medicine*, is by Kaji, Oseasohn, Jordon, and Dingle.[1] In this report entitled "Isolation of Asian Virus From Extrapulmonary Tissues in Fatal Influenza," the authors describe the isolation of Asian influenza virus from the lung or trachea, or both, in 25 of the 33 patients and from extrapulmonary tissues in 3 of these 25 patients who were shown to be respiratory-tract positive for the Asian virus. Virus isolations were carried out by means of the embryonated hen's egg, chiefly by amniotic inoculation, with verification by hemagglutination tests, and identification of the strain by specific antisera. Extrapulmonary tissues were available in 15 of the 25 respiratory-tract positive patients. Of particular interest to the authors was the isolation of the Asian strain of influenza virus from extrapulmonary organs in 3 of these 15 patients. In one instance the virus was detectable only in the tonsils; in the second instance, in the spleen and lymph nodes, and in the third, in liver, spleen, kidney, and heart. In the case in which virus was isolated from heart muscle no definite evidence of myocarditis could be demonstrated; only acute arteriolar lesions were present. These lesions consisted of fibrinoid degeneration of the arterioles with focal fibrin thrombi. On the other hand, no virus could be recovered from myocardial tissues in 3 patients in whom there was evidence of acute myocarditis histologically. It is of interest, likewise, that no virus could be detected in suspensions prepared from brain tissue of 2 patients who had shown clinical evidence of widespread central nervous system involvement during the illness.

Because of the unusally fulminating nature of this infection, the authors were interested in the possible role of viremia. Their studies indicated a relatively low concentration of virus in the extrapulmonary tissues. In the present series of cases the investigators did not undertake to demonstrate viremia but concluded from the presence of virus in organs distant from the respiratory tract that viremia probably occurs during overwhelming human infection. In this connection they refer to studies in experimental animals in which viremia could be detected and the presence of virus demonstrated in extrapulmonary tissues at autopsy. Hamre and her associates[2] were able to produce viremia in mice by intranasal inoculation or cloud-chamber exposure (Influenza A-PR8) and were able to recover the virus from extrapulmonary tissues, especially the liver and spleen.

The second report dealing with these fatal cases of Asian influenza is presented by Oseasohn, Adelson, and Kaji[3] in the *New England Journal of Medicine*, issue of March 12, 1959, and constitutes a clinicopathologic study of the 33 fatal cases of Asian influenza. These careful clinical and pathologic studies, together with the virus investigations reported by Kaji, Oseasohn, Jordan, and Dingle, reveal some interesting aspects of this important problem. Nineteen of the 25 respiratory deaths occurred in persons previously well; the remaining 6 gave evidence of pre-existing chronic cardiopulmonary disease. In 4 children the clinical course was characterized by convulsive seizures and coma without localizing signs, preceded by several days of mild respiratory symptoms. It was a striking observation that no evidence of encephalitis could be demonstrated in these children.

The fulminating course of this disease when associated with staphylococcus pneumonitis is exemplified by the case history of a 17-year-old boy who "caught cold" on November 16, 1957. An onset of ordinary upper respiratory symptoms was followed within 24 hours by extreme weakness and dyspnea. By the second day, bilateral pneumonia was apparent in this patient. Despite vigorous antibiotic therapy the boy died less than 2 days following the initial signs of upper respiratory infection which had simulated a "common cold." Asian influenza virus and hemolytic staphylococci were isolated from the lungs and trachea. Another case was that of a 17-year-old girl who developed chills, fever, and cough on October 5, and who was admitted to the hospital in shock on October 8; despite vigorous therapy the patient died 3 hours after admission. Postmortem examination revealed diffuse pulmonary involvement and interstitial myocarditis; the virus of Asian influenza was recovered from the lungs and trachea. Bacteriologic studies were negative in this case.

In the section on pathologic findings the authors emphasize that "generalized visceral and cerebral congestion is found almost universally in fatal influenza."[3] The typical lesion, however, is in the respiratory tract. Described as characteristic are the bulky, nonrepitant, hemorrhagic, and edematous lungs and the inflamed, necrotic air passages. Of interest from the standpoint of microscopic changes was the presence of an eosinophilic hyaline membrane outlining the alveolar spaces in 12 patients. In nonpneumonic areas hemorrhagic pulmonary edema was the outstanding feature, "the intrapulmonary and extrapulmonary air passages from terminal bronchiole to pharynx" being "inflamed in practically all patients."[3] The evidence of pre-existing cardiac abnormality in a total of 14 patients (of the 33) was also of considerable interest: 4 with inactive rheumatic heart disease, 1 with chronic cor pulmonale, and 9 with coronary arteriosclerosis or varying degrees of myocardial fibrosis or pure hypertrophy. The one virus-positive myocardium showed vascular lesions manifested by fibrinoid degeneration of arteriolar walls and focal fibrin thrombi. Three

of the 13 virus-negative samples of heart muscle gave histologic evidence of myocarditis. In the brain the most striking abnormalities consisted of a diffuse congestion and a generalized swelling manifested by flattening of the gyri. Even in those patients who had shown clinical evidence of diffuse central nervous system involvement, there were no signs of inflammatory disease of the brain. Changes in the lymph nodes ranged from simple edema and congestion to focal or diffuse areas of parenchymal hemorrhagic extravasation. The spleen was usually congested, with follicular changes accompanied by the deposition of fibrinous exudate. In the presently reported series the rapidly lethal course of Asian influenza in certain patients was brought into focus by 3 young persons who sought medical aid early in their illness and received symptomatic treatment at home. All 3 were transferred to the hospital a short time later in a moribund condition and died within a few hours.

The authors emphasize, in summary, that fulminant influenzal pneumonitis without superimposed bacterial infection does occur, although the importance of secondary bacterial invasion is well established, notably by hemolytic staphylococci, *Hemophilus influenzae*, and pneumococci. Treatment of these fulminating cases poses a serious problem since the course of the disease is so rapidly fatal that there is little opportunity for effective therapy. The general use of influenza vaccine is suggested as the only available means of decreasing this type of mortality. On the basis of these clinicopathologic studies and of those concerned with virus isolation, the authors feel that their investigations lend support to the concept of viremia in overwhelming influenza infection in man.

RUSSELL J. BLATTNER

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SIMPLIFIED METHOD OF INFANT FEEDING: BACTERIOLOGIC AND CLINICAL STUDY

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UNDOUBTEDLY the two questions mothers of artificially fed infants most frequently ask their physicians are: "How soon can I get the baby off of a formula?" and "How soon can I stop sterilizing the formula?"

This constant search for ease and simplicity is, of course, in keeping with the trend toward relieving young mothers of all possible excess work, as exemplified by diaper services, prepared infant foods, and, in some communities, central formula services.

Many attempts have been made in the past to answer this problem, but even the introduction of equipment designed to make home terminal sterilization comparatively simple has not served to answer the question.

To meet this demand, formulas consisting of equal parts of evaporated milk and water have been used by some physicians from as early an age as birth on. Others have felt that the younger infants need a more dilute formula and have persisted in the use of diluted formulas with added carbohydrate. The purpose of this study was not to test the relative values of different types of formulas but rather to determine whether under present-day urban conditions a simplified method for the preparation of formulas is clinically acceptable and bacteriologically safe.

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This paper and the following one by Gibson have been accepted for publication as evidences of current practices in the preparation of milk formulas which deviate from generally advised methods. The Editorial Board is not endorsing these practices but rather is making the pages of the JOURNAL available as a forum for adequate discussion and appraisal of this important subject. The reader is urged to consider carefully the data presented in the Letter from Fomon (p. 122) and the issues raised and views expressed in the editorial by Hill (p. 124).

METHOD

A "simplified" method of preparing individual feedings was then devised: (1) All bottles, nipples, spoons, and a funnel were thoroughly cleansed with a recommended household detergent and then thoroughly rinsed with HOT tap water. (2) Hot tap water in the amount specified for the individual infant was then run into the clean bottle. (3) If an added carbohydrate was desired, this was then added to the water and mixed well. (4) The specified amount of evaporated milk was next added with proper precautions as to cleansing and opening the can. (5) The nipple was then placed on the bottle and the infant fed as soon as possible thereafter. (6) The partly used can of evaporated milk was immediately placed in the refrigerator, to be used for the next feeding under the same technique; no milk was to be used from this can at a time longer than 24 hours after it had been opened. (7) It was stressed that any formula not consumed at a single feeding was to be discarded and *not* offered

to the baby at subsequent feedings. (8) Finally, it was cautioned that if the water was from any other source than a safe city or suburban water supply, the water was to be separately boiled for 5 minutes before using.

BACTERIOLOGIC SURVEY

To test the degree of bacteriologic growth when this method was employed, members of the Department of Microbiology of the Hahnemann Medical College under the supervision of Dr. Albert G. Moat prepared a number of bottles exactly as outlined above and then tested the contents at once and at 4 and 24 hours later for total bacterial counts and for the presence of lactose-fermenting coliform organisms. These studies were performed on formulas made with evaporated milk and hot tap water and with fresh homogenized A milk and hot tap water, with and without added carbohydrate.

CLINICAL TRIAL

After the bacteriologic studies had indicated that the method was potentially safe, it was offered to a number of mothers in private practice for use with their infants. The observations of the mothers were then evaluated on the basis of (1) their subjective reaction to the use of the method, (2) the gains in weight of the infants in comparison with those of a similar group on regularly sterilized formulas, and (3) the frequency of gastrointestinal disturbances in infants fed sterilized and nonsterilized formulas.

RESULTS

1. *Bacteriologic Studies.*—Single feedings prepared from sterile evaporated milk and hot tap water, immediately refrigerated, remained sterile for an indefinite period (beyond 24 hours). In contrast, those similarly prepared with homogenized grade A milk showed an increased bacterial count, although there was no evidence that these were pathogens. Even when kept at room temperature, bottles prepared as described above did not show any perceptible increase in bacterial count in 24 hours. When the bottles were similarly prepared and a powdered dextrin-maltose mixture was added, the bacterial count increased with standing, but no lactose-fermenting organisms were detected even after 8 hours at room temperature.

2. *Clinical Studies.*—All of the mothers (about 30) who volunteered to try this method expressed their gratification for the ease of preparation and considered it to be a significant time saver. The use of HOT tap water in the mixtures saved additional time since the necessity of reheating the bottle before feeding was eliminated. The gains in weight of infants fed formulas so prepared showed no statistical difference from those who received sterilized formulas. There were no evidences of gastrointestinal infection in either group.

DISCUSSION

It is evident that many mothers have discontinued the practice of sterilizing milk formulas even though they have been advised to prepare them by an aseptic technique.

Lathrop[2] found that the bacterial count in formulas prepared at home by different mothers using a powdered milk and carbohydrate mixture varied inversely with the cleanliness exercised by the mother and that, when part of a bottle was reused for a later feeding, the bacterial count rose greatly. These

observations served to strengthen our conviction that the presently suggested simplified method should be confined to SINGLE FEEDINGS, with all unused portions of each bottle to be discarded immediately.

Silver[3] after carefully reviewing the generally accepted methods of sterilization concluded that "there is no practical method of processing formulas so that sterility is insured in every bottle." He emphasized the dangers of possible breakdowns in the more commonly used aseptic method of preparation.

It may be that the simplified method of preparing *single* bottles of formula as described here may be as safe or safer than the various methods employed for preparing feedings for storage for periods of 24 to 48 hours. The so-called aseptic technique of preparation is especially vulnerable to contamination, and the potential of bacteria for multiplication in milk formulas is well recognized.

The authors wish to emphasize, however, that they do not recommend this method for infants in the hospital nursery or for premature or sick infants.

It would seem apparent also that the physician recommending the use of such a method must make sure that the mothers using it will follow instructions carefully—as, indeed, is the case with any method of formula preparation.

Lest there be objection to the use of standard household detergents for cleansing the bottles and nipples in the fear that significant quantities of this material might remain on the bottles and be toxic to the infant, the laboratories of the Pennsylvania Salt Manufacturing Company were asked to study this phase of the problem. Their report indicates that the concentration of detergent remaining after normal rinsing is far below an amount which might be considered to have a clinical effect.

SUMMARY

A simplified method of infant feeding using evaporated milk and HOT tap water from a city source, with or without added carbohydrates, has been subjected to bacteriologic and clinical testing.

These tests indicate that if the method outlined is carefully followed, single feedings so prepared are bacteriologically and clinically safe.

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IS FORMULA STERILIZATION NECESSARY?

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"How do you sterilize the formula?" I asked a young mother.

"I don't," she replied, "I simply mix the milk with water and give it to the baby. It agrees with him and he has not been sick. Should I sterilize the formula?"

After I had received this same response from other mothers, I began to wonder: How many mothers are following this practice? With modern handling of milk and water and with good refrigeration, is it possible that nonsterilized formulas may be safe for young infants? In searching the medical literature I could find no information to help answer these questions.

In order to obtain information on this problem I received the consent from the administrator of a local hospital to mail questionnaires to all mothers delivered in the months of February, March, and April, 1958. These were selected because their infants would range from 2 to 7 months of age during the hot Texas months of June, July, August, and September. I hoped to learn how these infants fared during this period on various methods of formula preparation. Since the mothers and the infants were in the care of many local physicians, the questionnaires were mailed from the Record Department, Hendrick Hospital, Abilene, Texas, with the return envelope addressed to it. No physician's name was included in the mailing, and the mothers were instructed not to sign their answered questionnaires. Of the 328 questionnaires mailed in October, 1958, 185 (56.4 per cent) completed ones were returned. The questions with answers are as follows:

What kind of milk has your baby been taking during the summer months? The answers were: homogenized milk, 77; evaporated milk, 42; breast milk, 19; breast milk and formula, 7; Similac, 6; soybean formulas, 6; SMA, 4; raw milk, 3; goat's milk, nonfat milk, Olac, Bremil, and Lactum, 1 each; unspecified milk, 16.

What kind of water has been used during the summer to make the formula? These answers were: city water, 127; distilled water, 10; country water (well, tank, cistern), 8; no water used, 3. The mothers who breast fed their infants and 18 others did not answer this question.

How has the formula been prepared during the summer months? One of the following methods was to be checked: (1) mix milk with water, no boiling or sterilizing; (2) bring water to boil, then mix with milk. These were followed by 12 other methods of formula preparation. The mother was instructed to describe her method if she could not find it listed. The most popular methods are given in Table I.

Do you always keep the prepared formula in an electric refrigerator? Of the 166 mothers who prepared formulas, 135 answered yes, 2 answered no, and 29 did not answer.

See footnote, p. 116.

How many attacks of diarrhea (very loose bowels) has your baby had? If your baby had diarrhea, was the baby mildly ill, moderately ill, or seriously ill? How many days (total) for all attacks of diarrhea? Did your baby go to the hospital for treatment for the diarrhea? The answers to these questions are given in Table II.

TABLE I. METHODS OF FORMULA PREPARATION FOR 185 INFANTS

METHOD	NUMBER AND PER CENT OF INFANTS
Terminal heat sterilization (25 minutes)	73 (39.4)
Formula not sterilized	49 (26.5)
Boiled water added to evaporated milk	22 (11.9)
Breast fed	19 (10.2)
Answers too varied to classify	22 (11.9)

Additional information as to the duration and severity of the diarrheas is given in Table III.

A study was made to determine what type of formula preparation was used for the infants who had diarrhea. The 31 infants who had had mild diarrhea for 1 to 7 days were omitted from this study, and attention was given to the 23 infants with more prolonged mild diarrhea (5) and to those with more severe diarrhea (18). Thirteen of the infants received formulas sterilized by the terminal heat method; 4 received formulas in which boiled water was added to evaporated milk; 1 was breast fed; 1 answer was too vague to classify; and 4 were on nonsterilized formulas. Of the 4 infants on nonsterilized formulas, 2 were on mixtures of evaporated milk and city water and 2 were on mixtures of evaporated or homogenized milk and country water.

TABLE III. DURATION AND SEVERITY OF DIARRHEA IN 54 INFANTS AS DESCRIBED BY MOTHERS

NUMBER OF INFANTS		DEGREE OF DIARRHEA	DURATION OF DIARRHEA (DAYS)
31	19	Mild	1 to 3
	12	Mild	4 to 7
23	5	Mild	8 to 60
	9	Moderate	1 to 7
	4	Moderate	8 to 14
	3	Moderate	30 to 45
	2	Serious	8 to 60
	0	Hospitalized	0

Note: The answers were too vague to classify in 6 cases; these were omitted.

TABLE II. OCCURRENCE OF DIARRHEA

FORMULA PREPARATION	NUMBER OF INFANTS	NUMBER AND PER CENT OF INFANTS WITH DIARRHEA	DIARRHEAS AS DESCRIBED BY MOTHERS			
			MILD	MODERATE	SERIOUS	HOSPITALIZED
Terminal heat	73	30 (41.1)	21	9	0	0
Nonsterilized formulas	49	14 (28.5)	10	4	0	0
Boiled water added to evaporated milk	22	5 (22.7)	1	2	2	0
Breast fed	19	5 (26.3)	5	0	0	0
Various other methods	22	6 (27.3)	2	2	0	0
Totals	185	60 (32.4)	39	17	2	0

Note: There were two cases of diarrhea not classified as to severity by the mothers. These were omitted.

What sugar or syrup do you add to the formula? Do you add the sugar or the syrup before or after sterilizing the formula? This was asked since some mothers might add a nonsterile syrup to a sterile formula. These questions were not answered by the 19 mothers who breast fed their infants or by 29 others. Of the 137 who answered, 71 did not use sugar or syrup in their formulas, 4 used sugar, and

62 used Karo syrup. The methods of adding Karo to the formulas and the corresponding diarrheal rate are given in Table IV.

TABLE IV. METHOD OF ADDING KARO TO 62 FORMULAS AND INCIDENCE OF DIARRHEA

KARO ADDED	NUMBER OF FORMULAS	NUMBER AND PER CENT OF INFANTS WITH DIARRHEA
Before sterilization	38	13 (34.2)
After sterilization	18	4 (22.2)
Unspecified	6	0

The incidence of diarrhea in these groupings does not vary significantly from the incidence of diarrhea for the entire group, which is 32.4 per cent.

DISCUSSION

It was surprising to discover that 49 (26.5 per cent) of the 185 mothers were giving nonsterilized formulas to their young infants. In most instances this consisted of mixing city water with either evaporated or homogenized milk. I asked several of the mothers why they followed this practice. They replied that they had heard of someone else who had given nonsterilized formulas to her infant without harmful results, so they adopted the practice. In no instance did they indicate that their physician had advised giving nonsterilized formulas.

Since the incidence of diarrhea did not vary markedly in this series in relation to the method of formula preparation, this indicates to me that it is necessary to look beyond the formula for the common causes of diarrhea. To focus attention too exclusively on the sterility of the formula is to think of only a small part of the infant's germ world. The baby will handle anything and then put his hands into his mouth. Pacifiers will be dropped frequently to the floor and then popped back into the baby's mouth. As one mother wrote on her questionnaire, "When the baby started crawling on the floor, I stopped sterilizing the formula." Probably no part of his environment can be sterile, but certainly all of it should be clean.

Sterilization of formulas was essential in the days when water and milk supplies were of doubtful purity and good refrigeration was scarce. Now the picture has changed, and we may wonder if formula sterilization is an outmoded ritual. The limited experience of these 49 mothers may point in that direction.

After making this study, I shall adopt a more relaxed attitude when a "clean" mother tells me that she has been giving a nonsterilized formula to her baby for months and he has been free of gastrointestinal upsets. I shall explain the potential dangers to her and also discuss other ways of preventing diarrhea. I shall warn her against placing her baby in a crowded or poorly supervised nursery where he would be exposed to others with respiratory and intestinal infections.

SUMMARY AND CONCLUSION

Information was assembled on formula preparation for 185 young infants during the summer months. The incidence of diarrhea did not appear to vary in infants receiving formulas prepared by various methods.

Correspondence

To the Editor:

In recent years there has been an increasing tendency to prepare formulas for infants without sterilization of bottles. In the hope of provoking an exchange of views on this subject we should like to report the results of bacteriologic studies of formulas prepared in various ways.

Mothers of small infants cooperating in other metabolic studies were asked to prepare an additional bottle of formula, ostensibly for chemical analysis. In almost all instances the women who participated were wives of undergraduate or graduate students living in the student housing areas of the State University of Iowa. Bottles were collected once each week during a 5-week period. One to five bottles were collected from each mother, as indicated in Table I. The bottles were prepared by the mothers in the morning or early in the afternoon. The bottles were not refrigerated for approximately 2 hours while the samples were being delivered to the hospital. The samples were then refrigerated until the next morning when a 10 ml. aliquot was transferred to a sterile container, delivered to the State Hygiene Laboratory, and cultured.

The methods of formula preparation used by the mothers are given in Table I and include three major categories: terminal sterilization; sterilization of bottles with or without sterilization of milk and water; and storage of formulas in unsterile bottles. None of the women used an automatic dishwasher. Three of the women leveled the amount of a commercially prepared powdered formula by brushing the finger across the top of the measuring utensil. The formulas prepared by the mothers using this technique have been classified as prepared by "finger leveling."

A coliform count using Difco dehydrated violet red bile agar and a standard plate count using Difco dehydrated tryptone glucose yeast agar were performed as outlined in the publication, Standard Methods for the Examination of Dairy Products, American Public Health Association (ed. 10). Coliform plates exhibiting any deviations from the standard criteria were further investigated as described in a previous report (Morris, R. L., and Cerny, J.: Significant Abnormalities in the Violet Red Bile Technique for Coliforms in Milk, Journal of Milk and Food Technology 17: 185, 1954). Several dilutions of the sample portions were set up for standard plate count so that the number of colonies on at least one plate would be between 30 and 300. However, in cases of gross bacterial growth in all dilutions the plate having the nearest to 300 colonies was selected for counting and estimation of number of colonies.

As may be seen from Table I, bacterial counts were greater when formulas were made or stored in unsterile bottles than when bottles were sterilized or terminal sterilization was performed. With one exception (participant 16), the bacterial counts were similar whether terminal sterilization or sterile bottles were used. Use of boiled or unboiled tap water did not appear to alter the results.

Even with terminal sterilization, 5 of 10 formulas had standard plate counts of more than 1,000 organisms per milliliter; however, no coliform organisms were isolated. Eight of the 17 formulas in sterile bottles also had standard plate counts of more than 1,000 organisms per milliliter but 5 of the formulas were prepared by the same mother (16), and only the formulas prepared by this mother had more than 90 coliform organisms per milliliter.

Formulas stored in unsterile bottles and those prepared with "finger leveling" almost uniformly contained high standard plate counts and 10 of 29 formulas had coliform counts greater than 1,000 organisms per milliliter.

pared by 3 women (1, 4, and 20) had counts at least as low as those of terminally sterilized formulas or formulas stored in sterile bottles. However, the generally higher bacterial counts in formulas stored in unsterile bottles suggests that it would

TABLE I. BACTERIAL COUNTS OF INFANT FORMULAS

MOTHER	NUMBER OF BOTTLES	STANDARD PLATE COUNT (ORGANISMS/ML.)			COLIFORM COUNT (ORGANISMS/ML.)			FEEDING AND REMARKS
		AVERAGE	HIGH	LOW	AVERAGE	HIGH	LOW	
				Terminal Sterilization				
9	2	10	10	0	0	0	0	CPL
14	2	60	60	0	0	0	0	CPL
17	1	235,000			0			CPP
19	4	42,043	72,000	170	0	0	0	CPL
21	1	7,500			0			CPL
				Sterile Bottles				
3	3	30	40	10	0	0	0	CPP, BW
6	2	170,000	249,000	91,000	45	90	0	CPP, TW
10	5	3,100	13,650	0	0	0	0	CPL, BW
15	2	60	110	10	0	0	0	CPP, TW
16	5	1,156,140	5,500,000	14,700	60,265	208,000	170	CPL, TW
				Unsterile Bottles				
1	3	300	630	50	0	0	0	CPP, BW
4	1	260			0			CPL, BW
5	1	468,000			730			CPL, TW
7	1	292,000			61			EM, TW
8	5	1,479,080	4,400,000	420	18,980	49,000	0	CPP, TW
13	3	202,700	318,000	69,000	5,005	74,000	18	EM, TW
18	2	4,395,000	8,000,000	790,000	24,730	49,000	460	CPP, TW
20	2	195	310	80	0	0	0	CPL, TW
				*Finger Leveling**				
2	3	3,039,815	7,700,000	99,450	9,400	24,500	57	CPP, BW
11	5	276,700	950,000	1,400	855	2,400	10	CPP, TW
12	3	1,041,665	2,360,000	30,000	59	160	0	CPP, TW

CPL = commercially prepared liquid formula.
CPP = commercially prepared powdered formula.
EM = formula of evaporated milk and water without added carbohydrate.
BW = boiled water.
TW = tap water (unboiled).
*Amount of powder in the measuring utensil was leveled off with finger; with one exception (2), the bottles were unsterile.

We should like to emphasize that the bacterial counts of all of the formulas undoubtedly increased significantly during the period of approximately 2 hours that elapsed from the time they were collected from the mothers until they were again refrigerated in the laboratory. In this sense the formulas are perhaps not representative of those ordinarily fed by these mothers to their infants. Six formulas prebe unwise to recommend this method of formula preparation for wide-scale use.

We hope that others who have considered this problem will record their results.

Samuel J. Fomon, M.D.
Lora N. Thomas, R.N.
Josephine Cerny, B.A.
Robert L. Morris, M.S.
Iowa City, Iowa

Editor's Column

FORMULA STERILIZATION

CRITICAL appraisal of long-established, "taken-for-granted" practices is highly desirable and probably should be undertaken more often than it is. Circumstances responsible for the initial establishment of a given practice may have changed or new knowledge may have been gained which justifies modification or even abandonment of a time-honored custom. Only when it is clear that the basic principles upon which the practice was founded are still applicable should change be resisted. As illustrations of some of these long-time practices which have come up for review in recent times, one might single out the performance of bleeding and clotting times preliminary to tonsillectomy and other surgical procedures, early versus late ambulation in rheumatic fever and acute nephritis, hot versus cold formulas in infant feeding, and bed rest verses ambulation in acute febrile illnesses.

Now the practice of formula sterilization, which for years has been considered an essential requirement for successful infant feeding, would appear to be up for scrutiny. The communications of Fischer and Whitman, of Gibson, and of Fomon in this issue are all directed toward this problem. Initially the Editors of the JOURNAL were somewhat reluctant to publish the papers, not because of the quality of the papers themselves but because of their fear that readers might gain the impression that formula sterilization was no longer necessary. However, when Gibson's study showed that over one fourth of an unselected group of mothers on their own volition were feeding nonsterile formulas to their infants, it was decided that a service could be accomplished by publishing the material and inviting comment by means of an editorial.

Those whose pediatric practices embraced the period when infant mortality and morbidity rates were high due to contaminated formulas will have strong misgivings about modifying or abandoning a practice which had more to do with the reduction of infant mortality and morbidity than any other single factor. They will want to be sure that any relaxation in requirements in an effort to lighten the mother's work load will not result in turning the wheels of progress backward rather than forward.

That conditions related to infant nutrition have changed markedly over the years cannot be denied. Practically all milk now offered for infant consumption in the United States is subjected to some form of heat treatment. Refrigeration is available in all but the poorest of homes. Most urban water supplies have been made bacteriologically safe by filtration processes and by the addition of chlorine.

Public health departments have accomplished much in promoting healthful environmental conditions, especially for the city dweller. Also, the over-all standard of living is vastly improved. Nevertheless, bacteria are still with us, and it would be naïve indeed to suppose that they would not quickly resume their former role if permitted to do so by any unwise relaxation in preventive measures which have proved their effectiveness over many years of clinical trial.

Unquestionably, there would be little risk of an infant's receiving an infected milk supply if the criteria set forth by Fischer and Whitman were followed exactly. To this extent, the simplified method of infant feeding recommended by them would be safe enough. But difficulties might be encountered when the method was spread by word-of-mouth from mother to mother rather than from physician to mother. For instance, the rural mother might not appreciate that the well or cistern water on her farm was not as safe as the hot tap water of her urban friend. Or the uninstructed mother might not understand the importance of immediate consumption of the formula following its preparation in nonsterile bottles from tap water. The data supplied by Fomon on the bacterial counts obtained from formulas in unsterile bottles unrefrigerated for two hours is informative in this respect. Even more impressive is the effect upon the bacterial count when mothers introduced bacteria into the formula by finger leveling of the powdered milk.

Still other questions arise. If the nonsterile technique of formula construction is advised, at what age may it be instituted—immediately after returning home from the hospital or at some later time such as at 1, 2, or 3 or more months of age? Can the newborn baby's drinking water safely be given from the tap in a nonsterile bottle or should this too be put off to a later age? Finally, there must come the question as to how much time is actually saved by the admittedly busy mother by preparing each feeding separately according to the method suggested by Fischer and Whitman over the terminal sterilization method in which bottles, nipples, formula, and drinking water can all be sterilized simultaneously? It would be our impression that the time saved would not be very great.

Because of the evidence that a degree of laxness may be creeping into the American scene in formula preparation as suggested by Gibson's study, it would appear urgent that more investigations be undertaken to determine whether the practice is safe under all conditions of infant feeding in homes, rural as well as urban, and by careless as well as careful mothers. For if a short cut is to be recommended, it is unrealistic to suppose it can be kept confined to one segment of the population.

LEE FORREST HILL

JOURNAL OF PEDIATRICS DOMESTIC LECTURESHIPS

THREE years ago the Editorial Board of the JOURNAL decided to use the Fund, established by the publishers for the "furthering of pediatrics," for visiting lectureships. Two types were suggested and discussed: One would bring distinguished pediatricians from abroad to spend a week at each of several pediatric clinics here. The other would provide a number of domestic lecturers to meet the special needs and desires of domestic pediatric clinics with teaching and research programs.

After considerable discussion with pediatric leaders and teachers, the decision was reached to try both types so that a program could ultimately be based on experience. The Foreign Lectureships and the modified program for 1959 were discussed in the April issue of the JOURNAL, page 359. Five domestic lecturers were programmed for 1958. Only four were scheduled for 1959 in order to increase the number of Foreign Lectureships available for the year of the International Pediatric Congress in Montreal.

For 1959, the clinics and lecturers selected for the Domestic Lectureships, together with the purpose of each lectureship, are as follows:

University of Alberta, Edmonton, Canada: Dr. John P. Hubbard, Philadelphia (social and preventive pediatrics).

University of Oklahoma, Oklahoma City, Okla.: Dr. Clement A. Smith, Boston (newborn service).

University of Louisville, Louisville, Ky.: Dr. T. F. McNair Scott, Philadelphia (clinical investigation).

Tulane University, New Orleans, La.: Dr. Douglas Buchanan, Chicago (pediatric neurology).

The results of the first trial year of the Domestic Lectureships were most encouraging and tend to lead the Foundation to feel that they meet a definite educational need. The number for 1960, therefore, has been increased to 6. A total of 15 over a 3-year period should provide a satisfactory experience for basing a final judgment of their need and desirability.

Of the 1958 lectureships, one department head wrote, "He gave us much needed insight into our problems." Another said, ". . . all members of our department had a truly unique opportunity to spend time with him . . . general rounds by Dr. 'X' with our entire pediatric faculty and about 100 out-of-town pediatricians." To quote a third, "We have just completed one of the most productive weeks in the relatively short life of our department. In my opinion the project of making such visiting professorships available is the finest type of philanthropy that can be carried out in medical education."

The president of one of the universities wrote, "I met Dr. 'Y' several days ago and had a chance myself to appreciate the wisdom and stimulation he has brought to our pediatric staff. We do appreciate the assistance which

the Journal of Pediatrics Educational Foundation has given to Pediatric education in this area by making it possible for Professor 'Y' to be here." From a letter from the dean of one medical school, "During his visit Dr. 'Z' contributed richly to our total pediatric program, serving as a real source of stimulation and information not only to our medical students and house staff but to junior and senior staff members." One of the 1958 lecturers made a request for a 1959 lectureship for his own department.

One of the more encouraging experiences with the Domestic Lectureships has been that all 9 of the lecturers suggested by the clinics have accepted the invitation of the Foundation. Without such wholehearted interest on the part of our topflight pediatric teachers and scientists, a Domestic Lectureship program would falter. One of the most interesting aspects revealed in the lectureships has been the wide variety of purposes, reflecting the broad interests of pediatrics. In addition to the four mentioned above, the purposes have included child psychiatry, the teaching of clinical pediatrics and of the infectious diseases, a rehabilitation program, and departmental organization.

Announcements of the Foreign and Domestic Lectureship program for 1960, inviting chiefs of staff to make requests for lectureships, will be sent to the pediatric clinics in the United States and Canada later this year. From these requests the Foundation trustees—a rotating committee of 3 members of the Editorial Board with a new member each year—will select the clinics. Once the clinics and lecturers are settled, the Foundation withdraws except for financial responsibility. All details, such as the lecturer's program for the week and in the case of the domestic lecturer the week of lectureship, are arranged directly between the chief of staff of the clinic and the lecturer.

B. S. V.

News and Notes

The following pediatricians were certified by the **American Board of Pediatrics, Inc.**, on May 2, 3, and 4, 1959, in Philadelphia, Pennsylvania.

Dr. Milton Alvarez-Pagan, 563 Independencia St., Baldrich, San Juan, Puerto Rico.

Dr. Natalie Aronson, 7154 Washington Ave., University City 5, Mo.

Dr. Mary Ellen Avery, 296 Beacon St., Boston 16, Mass.

Dr. Donald R. Berman, 174 Central St., Lowell, Mass.

Dr. Arnold Blake, 122 Pleasantview Ave., Longmeadow, Mass.

Dr. Joseph R. Bongiorno, 1337 82nd St., Brooklyn 28, N. Y.

Dr. Marie J. Browne, 333 Cedar St., New Haven 11, Conn.

Dr. Albina Angela Claps, 61-15 76th St., Rego Park 79, Queens, N. Y.

Dr. Margaret Thomson Colgan, 75 Fonthill Park, Rochester 18, N. Y.

Dr. Thomas Edwin Cook, 120 South Parking Place, Lake Jackson, Texas.

Dr. Henry Gaylord Cramblett, University Hospitals, Iowa City, Iowa.

Dr. Peter Ritsher Cunningham, Moose Hill Road, Guilford, Conn.

Dr. Charles Pelham Curtis, Jr., Hulls Highway, Southport, Conn.

Dr. Elisabeth Burnett Decker, 617 West 168th St., New York 32, N. Y.

Dr. Elaine K. Donnellan, 300 Longwood Ave., Boston, Mass.

Dr. Jacques-Raymond Ducharme, 68 Morris St., Yonkers 5, N. Y.

Dr. Richard T. Ellison, Jr., 669 Pine Tree Road, Jenkintown, Pa.

Dr. John F. Faigle, Jr., Main Street, Stony Brook, N. Y.

Dr. Willard Barker Fernald, 2687 Columbus Ave., Columbus, Ohio.

Dr. Jerome H. Finck, 20288 Westbrook, Detroit 19, Mich.

Dr. John Apfel Fisher, Pennsylvania Hospital, 8th & Spruce Sts., Philadelphia, Pa.

Dr. Stephen M. Frawley, 1180 Beacon St., Brookline 46, Mass.

Dr. David R. Gair, 6880 Coral Way, Miami 55, Fla.

Dr. Mary Zonger Gasparik, 330 East 80th St., New York 21, N. Y.

Dr. Gustave Gavis, P. O. Box 584, Monticello, N. Y.

Dr. George Wallen Greenman, 97 Sherman Ave., New Haven, Conn.

Dr. Louis Guss, 59 Sachem St., Norwich, Conn.

Dr. William S. Gyves, 1020 Lorimer St., Brooklyn, N. Y.

Dr. Louis Leighton Hill, Babies and Children's Hospital, 2065 Adelbert Road, Cleveland, Ohio.

Dr. Milos A. Jansa, 7403 Yarnum St., Landover Hills, Md.

Dr. Seymour H. Kaplan, 15 Bond St., Great Neck, N. Y.

Dr. Mufit Husam Kesim, Central State Hospital, Lakeland, Ky.

Dr. Stella B. Kontras, 3090 Livingston Ave., Columbus 9, Ohio.

Dr. Herbert Irving Lerner, 727 E. 60th St., Chicago 37, Ill.

Dr. Ruth Geyer Lerner, 727 E. 60th St., Chicago 37, Ill.

Dr. Mary Jane Luke, 3695 University Station, Charlottesville, Va.

Dr. Noble T. Macfarlane, Jr., 1221 South Broadway St., Lexington, Ky.

Dr. Murray G. McGovern, 157 Dundas St. North, Oakville, Ontario, Canada.

Dr. William T. McLean, Jr., Jefferson Medical College, 1025 Walnut St., Philadelphia 7, Pa.

Dr. Thomas P. Mahaney, 212 South Granger St., Saginaw, Mich.

Dr. Herbert C. Mansmann, Jr., 213 Lexington Ave., Pittsburgh 15, Pa.

Dr. William J. Mellman, 3400 Spruce St., Philadelphia 4, Pa.
Dr. Fred Neal Mitchell, 229 N. Torrence St., Charlotte 4, N. C.
Dr. Rebecca F. Notterman, 564 S. Main St., Hightstown, N. J.
Dr. Walter B. Omans, 2600 N. Lawrence St., Philadelphia, Pa.
Dr. Mary Louise Pfaff, 1230 Pleasantville Road, Briarcliff Manor, N. Y.
Dr. Michael E. Salomone, 197 Ridgecrest Ave., Staten Island, N. Y.
Dr. Anna Sandberg, 314 Angell St., Providence 6, R. I.
Dr. Samuel Selby, Box 144, Fairfield Pike, Yellow Springs, Ohio.
Dr. Samuel Norman Sherry, 4 Fernald Drive, Cambridge, Mass.
Dr. Anneliese L. Sitarz, 69 Edgewood Road, Summit, N. J.
Dr. Arthur Charles Smid, 551 White Oak Drive, Naperville, Ill.
Dr. James D. Stuart, 447 Atwater, Elmhurst, Ill.
Dr. Irwin Thomas Taylor, Carswell USAF Hospital, Fort Worth, Texas.
Dr. Charles T. Tuke, 4300 St. Paul Blvd., Rochester 17, N. Y.
Dr. Harold H. Wagner, 366 South Oyster Bay Road, Hicksville, N. Y.
Dr. Robert Owen Walton, 19406 Wickfield Ave., Cleveland 22, Ohio.
Dr. Norman Weinstein, 17 Greenbrier Circle, Fairfield, Conn.
Dr. Donald Richard Weymann, 35 Manor Road, Smithtown, N. Y.
Dr. Bernard A. Yablin, 1815 South Salina St., Syracuse 5, N. Y.
Dr. Ruth Priscilla Zager, 5100 Lebanon Ave., Philadelphia 31, Pa.

SPECIAL FOREIGN CERTIFICATE

Dr. James Shi-chow Tang, New York Medical College, One East 106th St., New York 29, N. Y.

The Department of Pediatrics of the **University of Colorado Medical Center** is offering one or two year pediatric fellowships for 1960 and 1961 in allergy, infectious disease, hematology, and premature and newborn infant nursery. The fellowships include fundamental laboratory research and clinical investigation as well as training in clinical diagnosis and management.

Applicants should be graduates of approved medical schools and should have completed at least one or more years of hospital training. Preference will be given to those in the course of completing the pediatric hospital training required for the examination of the American Board of Pediatrics.

Inquiries should be sent to Henry K. Silver, M.D., University of Colorado Medical Center, 4200 East Ninth Ave., Denver 20, Colo.

The Department of Pathologic Anatomy of **The Children's Hospital of Philadelphia** announces a residency program in pediatric pathologic anatomy open to residents in general pathology who have completed their second year of formal training in pathologic anatomy. The American Board of Pathology has approved the program toward eligibility for its examination.

It is anticipated that appointments will be made to begin on or about July 1 of each year. Applications should be sent to Dr. William C. Yakovac, Director of Pathology, The Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

The **Johns Hopkins University** has a position open in a research laboratory concerned with the pathology of pregnancy and newborn infants. This would be suitable for a pediatrician, an obstetrician, or a pathologist. There will be an opportunity for doing research independently or in collaboration with a senior staff member. The person should also serve as liaison between research in the laboratory and in the clinical service. Those interested should write to Dr. Peter Gruenwald, Department of Obstetrics, The Johns Hopkins Hospital, Baltimore 5, Md.

The Editors of *Modern Medical Monographs* announce the 1959 annual competition for unpublished manuscripts on clinical subjects in the field of internal medicine to stimulate young graduate physicians under 40 to communicate their work in the classical form of the monograph and to achieve high standards of medical writing.

First prize will be $500.00. Authors of top-ranking manuscripts found suitable will be offered a contract for publication in the

series *Modern Medical Monographs* under standard royalty arrangements, published by Grune and Stratton, Inc.

Entries will be judged for style and clarity by a committee of the American Writers' Association and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monographs.*

Manuscripts must be postmarked no later than October 1, 1959.

For additional regulations, write to Dr. Irving S. Wright, 450 East 69th St., New York 21, N. Y.

The American Academy for Cerebral Palsy's officers for 1959 are Alvin J. Ingram, M.D., President; Raymond R. Rembolt, M.D., President-Elect; Temple Fay, M.D., Vice-President; Glidden L. Brooks, M.D., Secretary; and Samuel B. Thompson, M.D., Treasurer. The Academy's annual meeting is to be from November 30 through December 2 in Los Angeles.

Books

Pediatric Neurology. Stanley S. Lamm, New York, 1959, Landsberger Medical Books, Inc., 495 pages. Price $12.50.

This monograph reviews the subject satisfactorily and is clearly written. It supplements rather than replaces the standard text, Ford's "Diseases of the Nervous System in Infancy, Childhood, and Adolescence," by being less formidable and more didactic. Unfortunately, simplification in many places gives rise to dogmatic statements that are open to question or to qualification. In several places the reader is assumed to be on familiar ground and to need no further help. For example, the paragraph on the treatment of status epilepticus is too short to be helpful. However, each subject is reviewed with considerable skill, and the bibliography gives carefully selected references which are current and for the most part readily accessible. This text represents the opinion of a well-informed clinician on a variety of subjects and is a welcome addition to a field of increasing interest.

Henry W. Baird III.

Therapeutic Radiology. William T. Moss, M.D., St. Louis, 1959, The C. V. Mosby Co., 402 pages. Price $12.50.

This book represents a valuable and thorough approach to the subject of radiotherapy and is written in a concise and readable style. Throughout the book Dr. Moss emphasizes the rational rather than the technical details of radiotherapy, acknowledging the fact that in all forms of radiotherapy, regardless of the condition under treatment, the approach must be individualized and that a precise statement regarding dosage cannot be made. However, the usual duration of treatment as well as amount of radiation for the many various conditions under discussion are given in sufficient detail to satisfy the student who is undergoing training in radiotherapy. The book is divided into twenty chapters dealing with radiation therapy of the skin, the oral cavity and oral pharynx, the orbit, the ear, nasopharynx, nasofossa and paranasal sinuses, the endolarynx and hypopharynx, the esophagus, the lungs, the breast, the stomach and small bowel, the kidney, the urinary bladder, the testicle, the cervix, the endometrium, the ovary, the hemopoietic tissues, the bone, the brain, the spinal cord and peripheral nerves, and selected soft tissue tumors. A splendid introduction is offered which deals with the rational of therapeutic radiology and the relationship between the radiotherapist and his clinical associates. Dr. Moss's book should prove of value to the physician training in radiotherapy as well as to the experienced physician in this field. It is practical, well-written, and a thoroughly enjoyable study of the subject.

Edward B. Singleton, M.D.